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Original Articles

Pseudoexfoliation Syndrome and Antidepressant Drug Use
Erdoğan Yaşar et al; Aksaray, Eskişehir, Turkey

Evaluation of the Effect of Body Position on Intraocular Pressure Measured with Rebound Tonometer
Hüseyin Mayalı et al; Manisa, Turkey

Etiological and Clinical Characteristics of HLA-B27-associated Uveitis in a Tertiary Referral Center
Merve İnanç et al; Van, Ankara, Turkey

First-Year Outcomes of Cataract Surgery Combined with Intravitreal Ranibizumab Injection in Wet Age-Related Macular Degeneration
Sabahattin Sül et al; Muğla, Turkey

The Effect of Smoking on Macular, Choroidal, and Retina Nerve Fiber Layer Thickness
Kuddusi Teberik; Düzce, Turkey

Approach of Family Physicians to Pediatric Eye Screening in Diyarbakır
Zeynep Gürsel Özkurt et al; Diyarbakır, Turkey

Review

Current Therapeutic Approaches to Chronic Central Serous Chorioretinopathy
Samet Gülkaş and Özlem Şahin; Şanlıurfa, İstanbul, Turkey

Case Reports

Central Serous Chorioretinopathy: A Complication Associated with Behçet's Disease Treatment
Nur Doğanay et al; İzmir, Turkey

Staphylococcus epidermidis Endophthalmitis Masquerading as Panuveitis After an Imperceptible Ocular Trauma
Juan Martin Sanchez et al; Jerusalem, Israel

Periorbital Emphysema After Endoscopic Nasal Polyp Surgery
Esat Çınar et al; İzmir, Turkey

Pneumatic Displacement of a Dense Sub-inner Limiting Membrane Pre-macular Hemorrhage in Dengue Maculopathy: A Novel Treatment Approach
Ashok Kumar et al; New Delhi, India

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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter. Internationally accepted abbreviations should be used; refer to scientific writing guides as necessary.

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CONTENTS

Original Articles

1 Pseudoexfoliation Syndrome and Antidepressant Drug Use
Erdoğan Yaşar, Nilgün Yıldırım, Eray Atalay; Aksaray, Eskişehir, Turkey

6 Evaluation of the Effect of Body Position on Intraocular Pressure Measured with Rebound Tonometer
Hüseyin Mayalı, Beyza Tekin, Özcan Rasim Kayıkçıoğlu, Emin Kurt, Süleyman Sami İlker; Manisa, Turkey

10 Etiological and Clinical Characteristics of HLA-B27-associated Uveitis in a Tertiary Referral Center
Merve İnanç, Mert Şimşek, Müge Pınar Çakar Özdal; Van, Ankara, Turkey

15 First-Year Outcomes of Cataract Surgery Combined with Intravitreal Ranibizumab Injection in Wet Age-Related Macular Degeneration
Sabahattin Sül, Aylin Karalezli, Müjdat Karabulut; Muğla, Turkey

20 The Effect of Smoking on Macular, Choroidal, and Retina Nerve Fiber Layer Thickness
Kuddusi Teberik; Düzce, Turkey

25 Approach of Family Physicians to Pediatric Eye Screening in Diyarbakır
Zeynep Gürsel Özkurt, Selahattin Balsak, Mehmet Sinan Çamçi, Kadir Bilgen, İbrahim Halil Katran, Adar Aslan, Çağla Çilem Han; Diyarbakır, Turkey

Review

30 Current Therapeutic Approaches to Chronic Central Serous Chorioretinopathy
Samet Gülkaş, Özlem Şahin; Şanlıurfa, İstanbul, Turkey

Case Reports

40 Central Serous Chorioretinopathy: A Complication Associated with Behçet's Disease Treatment
Nur Doğanay, Melike Balıkoğlu Yılmaz, Betül Orduyılmaz, Erdinç Aydın, Ali Osman Saatçi; İzmir, Turkey

44 *Staphylococcus epidermidis* Endophthalmitis Masquerading as Panuveitis After an Imperceptible Ocular Trauma
Juan Martin Sanchez, Diego Almeida, Tareq Jaouni, Radgonde Amer; Jerusalem, Israel

47 Periorbital Emphysema After Endoscopic Nasal Polyp Surgery
Esat Çınar, Berna Yüce, Murat Fece, Fehmi Cem Küçükerdönmez; İzmir, Turkey

51 Pneumatic Displacement of a Dense Sub-inner Limiting Membrane Pre-macular Hemorrhage in Dengue Maculopathy: A Novel Treatment Approach
Ashok Kumar, Vikas Ambiya, Vinod Kumar Baranwal, Amit Arora, Gaurav Kapoor; New Delhi, India

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EDITORIAL

2019 Issue 1 at a Glance:

This issue of our journal comprises 6 original research articles, 1 review, and 4 case reports selected from among the studies conducted by ophthalmologists both nationally and internationally to protect and improve human health.

Yaşar et al. present an epidemiological study investigating the relationship between pseudoexfoliation syndrome (PES) and antidepressant drug use. Their survey of systemic diseases and medication use conducted among 2017 individuals revealed that antidepressant drug use was more common in the PES group. The authors pointed to the common role of oxidative damage and inflammation caused by free radicals in the pathogenesis of both PES and depression, and suggested that inflammation induced by the accumulation of pseudoexfoliative material in the brain could trigger depression, thus resulting in higher rates of antidepressant drug use in PES patients (see pages 1-5).

In a study by Mayalı et al. evaluating the effect of body position on intraocular pressure (IOP), no statistically significant differences were detected in IOP values measured in 52 patients in sitting, standing, and supine positions using the Icare PRO tonometer. Age and gender also had no effect on IOP measured in the different body positions. Based on these results, the authors concluded that the Icare PRO could be used reliably to monitor IOP during clinical follow-up of patients with limited mobility, such as those who are bedridden (see pages 6-9).

The most common form of uveitis, or intraocular inflammation, is anterior uveitis. HLA-B27-associated uveitis is the most common etiology of anterior uveitis overall and especially presentations with hypopyon. In spite of ongoing research, the pathogenesis of HLA-B27-associated uveitis is not fully understood. Patients with HLA-B27-associated uveitis show variation in their clinical features, response to treatment, and systemic comorbidities. In their study investigating the demographic, etiologic, and clinical characteristics of HLA-B27-associated uveitis, İnanç et al. report that this type of uveitis is characterized by sudden-onset anterior segment inflammation with unilateral or alternating bilateral involvement and limited duration. They also report that uveitis may be associated with certain systemic diseases, especially ankylosing spondylitis, and visual prognosis is good despite complications (see pages 10-14).

Sül et al. investigated first-year outcomes in patients with active neovascular age-related macular degeneration (nAMD) who did and did not have cataract surgery while under intravitreal ranibizumab (IVR) therapy. The authors report that cataract surgery resulted in significant visual gains in patients receiving anti-VEGF therapy without adversely affecting AMD progression. They concluded that anti-VEGF therapy combined with cataract surgery could be considered a safe and effective treatment method in patients with active nAMD (see pages 15-19).

Smoking is a known risk factor for the development of certain ocular pathologies, including AMD, ischemic optic neuropathy, hypertensive retinopathy, cataract, glaucoma, and thyroid orbitopathy. In a study by Kuddusi Teberik, spectral domain optical coherence tomography (SD-OCT) was used to compare macular, choroidal, and retinal nerve fiber layer (RNFL) thicknesses in smokers and healthy non-smokers. Their analysis showed that RNFL thickness is reduced in chronic smokers, while macular and choroidal thickness were not affected (see pages 20-24).

Eye and vision screening is included within the responsibilities of infant/child follow-up in the preventive medicine services provided by family physicians in Turkey. Gürsel Özkurt et al. evaluated family physicians' approach to eye and vision screening in the province of Diyarbakır by conducting a 16-question survey with 100 family physicians working in the urban center and surrounding districts. While 88% of the physicians who participated in the survey stated that they knew the red reflection screening test, only 16% conducted it regularly and 36% said they did red reflex examination only if a problem was suspected. It was also determined that many of the physicians did not know the proper timing of treatment and did not refer patients to an ophthalmologist in a timely manner if they did detect a problem, and some centers were not equipped with basic instruments such as an ophthalmoscope. The authors concluded by emphasizing the significant lack of information on this public health issue and reported that it would be useful to conduct educational seminars on the subject (see pages 25-29).

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EDITORIAL

The review by Gülkaş and Şahin entitled "Current Therapeutic Approaches to Chronic Central Serous Chorioretinopathy" examines available treatment options when CSCR, which is characterized by serous neurosensorial retinal detachment and typically has good prognosis, deviates from its usual clinical course and becomes chronic. The authors provide valuable information about this issue, for which various therapies have been tried in recent years, including verteporfin-photodynamic therapy (PDT) with different parameters (standard protocol, half-dose, half-fluence PDT), anti-vascular endothelial growth factors, glucocorticoid antagonists, mineralocorticoid receptor antagonists, and subthreshold micropulse laser (see pages 30-39).

In the first case report of the issue, Doğanay et al. present two patients with CSCR accompanying Behçet's disease. They suspected systemic steroid use as the main culprit behind this association and emphasized the need to consider CSCR in patients who report a decline in vision while under steroid therapy (see pages 40-43).

In another interesting case report in this issue, Sanches et al. describe a case of *Staphylococcus epidermidis* endophthalmitis presenting as panuveitis following an unrecognized ocular trauma. Based on this case, the authors point out the need to properly evaluate posttraumatic patients with unremarkable findings and obtain a comprehensive history due to the possibility of hidden adverse effects (see pages 44-46).

Çınar et al. report a patient who developed periorbital emphysema after endoscopic nasal polyp surgery. Their report brings attention to the fact that although this complication is rare, it may require urgent intervention due to the possibility of increased IOP and disrupted circulation due to pressure exerted on the globe by the trapped subcutaneous air (see pages 47-50).

Kumar et al. describe the recent case of a 24-year-old patient on active military duty who was being treated for dengue hemorrhagic fever and presented with severe visual impairment in his right eye. Examination revealed sub-ILM hemorrhage in his right (dominant) eye. Dengue fever is an acute viral (Flavivirus) infection transmitted by mosquito bite, and infected patients can have diffuse ocular findings as well as rare cases of premacular hemorrhage. Considering the potential risks of steroid therapy and vitrectomy, and because time was of the essence to the patient due to his profession, he was treated with pneumatic tamponade with prone positioning. The authors report that this novel treatment may be a useful method to be considered for patients who are not eligible for active surgical treatment (see pages 51-54).

Respectfully on behalf of the Editorial Board,
Tomris Şengör, MD

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Original Article

Pseudoexfoliation Syndrome and Antidepressant Drug Use

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Abstract

Objectives: To investigate the relationship between pseudoexfoliation syndrome (PES) and the use of antidepressant medications.

Materials and Methods: This population-based, cross-sectional study included 2,017 of 2,356 invited subjects who were randomly selected from the Turkish Statistical Institute database (www.turksat.gov.tr/) as part of an epidemiologic study which specifically aimed to detect the prevalence of PES in the province of Eskişehir. During the examination, a detailed questionnaire was administered to determine physician-diagnosed systemic disease and drug use.

Results: Eight of the 2,017 participants in the study were excluded for various reasons (2 with posterior synechiae, 2 with corneal opacity, 1 uncooperative patient, 1 eviscerated patient, 1 with active adenoviral keratoconjunctivitis, and 1 with a history of angle closure). PES was detected in 100 (5%) of the 2,009 patients whose data were analyzed. The percentage of subjects with concurrent antidepressant drug use in the PES and non-PES non-glaucoma groups were 4.1% (n=3) and 1.1% (n=21), respectively. The difference between the two groups was statistically significant (p=0.024). In addition, the use of medications for hypertension (p<0.001) and coronary artery disease (p=0.009) was also higher in the PES group.

Conclusion: The higher prevalence of antidepressant drug use in patients with PES may be related to the processes of vascular damage and inflammation common to the pathogenesis of both PES and depression, as well as the high rate of chronic systemic comorbidities in these patients.

Keywords: Pseudoexfoliation, depression, antidepressant drug

Introduction

Pseudoexfoliation syndrome (PES), first described by Lindberg in 1917, is a clinical entity characterized by the accumulation of gray-white extracellular fibrillary material in the anterior segment tissues of the eye.[1,2] Besides the eye, exfoliative material (EM) has also been detected in the heart, lung, liver, kidney, and meninges using light/electron microscopy and immunohistochemical/biochemical methods.[3,4]

Oxidative damage and inflammation caused by free radicals has been shown to have a role in the pathogenesis of PES.[5,6,7] Increased oxidative stress and subsequent impairment of cellular immunity through the proteasome system are believed to be instrumental in the pathogenesis of PES.[1] Electron microscope studies of iris tissue samples from patients with PES have demonstrated EM deposition and damage to the iris vessels.[8,9] Furthermore, histopathological examination of samples obtained from PES patients with aortic aneurysm revealed focal accumulation of EM, pronounced fibrosis, and tunica intima elastosis in the adventitial and subendothelial connective tissue.[10] A recent genetic study identified five novel loci associated with predisposition for PES and the risk ratio for one of these loci varied by geographical latitude (increasing toward the polar regions).[11]

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PES is a clinical condition that increases in frequency in individuals over the age 50 and with increasing age.[12] Various studies have shown that the incidence and prevalence of PES varies in different populations, even within the same population in different regions, and its frequency varies between 0% and 38%.[13]

In addition to secondary glaucoma, cataract, and complications related to cataract surgery, PES patients have higher rates of hypertension (HT), coronary artery disease (CAD), heart attack, stroke, Alzheimer's disease, peripheral vascular diseases, and hearing loss, illustrating the systemic character of PES.[14,15,16,17,18,19,20] In addition, a study comparing patients with pseudoexfoliation glaucoma (PXG), primary open-angle glaucoma (POAG), and a control group showed that depression was significantly more common in the pseudoexfoliative group while the POAG and control groups had similar rates of depression, suggesting that PES may be associated with depression.[21] The aim of this study was to investigate the relationship between PES and depression and other systemic diseases based on survey results from our population-based cross-sectional PES prevalence study.

Materials and Methods

The study was carried out in accordance with the principles of the Declaration of Helsinki and ethical approval was obtained from the Ethics Committee of Eskişehir Osmangazi University (7 February 2013, project number: 06). This population-based randomized study was part of an epidemiological study to determine the prevalence of PES in Eskişehir, Turkey, a city covering 2,678 km^2 with a population of 826,716.[22] Randomization was done with a centralized method using the Turkish Statistical Institute database. This database contains regularly updated address information for all residents of Eskişehir. The target population consisted of people aged 40 and over living in the urban center and rural areas of Eskişehir.

A layered two-stage cluster sampling method was used for randomization and the study was conducted between 15 June and 1 October 2014 using the most recent information from February 2014. In the first sampling phase, clusters of approximately 100 households were probability sampled in proportion to their size. In the second phase, 10 households were randomly selected from each cluster using systemic sampling. Residence data for the selected households were obtained from local archives. People aged 40 years and over who resided in the randomly selected households were contacted through the neighborhood representative and invited to participate in the study. Brochures explaining the purpose of the study and information about the disease were given to neighborhood representatives to deliver to these individuals. Examinations were conducted between June and October 2014 and informed consent was obtained from all participants.

The subjects were examined in the ophthalmology outpatient clinic of the Eskişehir Osmangazi University School of Medicine. Data pertaining to the participants' demographic and social characteristics, general and ocular medical histories, and regular drug use were collected in face-to-face interviews by a nurse who was knowledgeable about the study and survey methods. Participants were questioned about all drugs they were currently using. Anterior segment examination was performed by an experienced resident physician (E.Y.) using a photobiomicroscope (Topcon-sl-D7, SN:1613331, Japan). Intraocular pressure was measured with an Icare tonometer; the average of 5 measurements provided by the device was recorded for both eyes. In terms of glaucoma, all patients underwent fundus examination (cup-to-disc [C/D] ratio) and Humphrey visual field test when necessary for diagnosis. Glaucomatous optic neuropathy was defined as neuroretinal rim loss with vertical C/D ratio ≥0.7 or vertical C/D ratio asymmetry >0.2 between the two eyes and/or visual field defect typical of glaucoma and consistent with focal notching of the neuroretinal rim. Both pupils were then dilated using mydriatic drops (0.1% tropicamide). Thirty minutes after instillation, the lens and other anterior segment structures were re-evaluated for pseudoexfoliation and photographed. PES diagnosis was made in the presence of white-gray EM on the pupil margin and lens anterior capsule. Images of patients with diagnosed or suspected PES were evaluated by the glaucoma consultant for confirmation (N.Y.).

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0 (SPSS, Inc., Chicago, IL). A t-test was used to compare numerical variables and chi-square test was used to compare the distribution of categorical variables between groups. Statistical significance was accepted as $p<0.05$.

Results

Of the 2,356 people who were randomly selected and invited to the study, 2,017 (85.6%) participated. Eight of the 2,017 participants (2 with posterior synechiae, 2 with corneal opacities, and 4 who were uncooperative, had one eviscerated eye, had adenoviral conjunctivitis, or had history of narrow-angle glaucoma) were excluded from the analysis. Demographic characteristics of the individuals with and without PES who were included in the study are summarized in Table 1.

PES was detected in 100 (5%) of the 2,009 participants. The mean age of the 100 people with PES was 69.1±9.9 years and that of the individuals without PES was 59.2±10.9 years ($p<0.001$).

After 33 glaucoma patients were excluded from 1,909 non-PES subjects, antidepressant drug use was reported by 21 (1.1%) of the remaining 1,876 subjects (mean IOP: 14.7±3.4 mmHg). After 26 glaucoma patients were excluded from 100 subjects with PES, antidepressant drug use was reported by 3 (4.1%) of the remaining 26 subjects (mean IOP: 14.1±3.3 mmHg). There was no statistical difference in mean IOP between the groups, whereas the incidence of antidepressant use was significantly higher in patients with PES ($p=0.024$, Table 2). Details regarding the physician-prescribed antidepressant drugs are shown in Table 3.

In addition, the results of the survey questions regarding physician-diagnosed disease and drug use revealed that of the 1,909 non-PES subjects, 626 (32.8%) used antihypertensive drugs and 162 (8.5%) used medication for CAD. These rates were significantly higher in the 100 subjects with PES, with 48% using antihypertensive drugs (p<0.001) and 17% taking medication for CAD (p=0.009). No significant difference was found between the groups in terms of drugs used for other diseases (p>0.05) (Table 4).

Discussion

In our study, PES was detected in 100 of 2,009 individuals evaluated (5%). Other studies of PES prevalence in the Turkish population reported rates in the 7-12% range, higher compared to our population-based randomized study.[23,24,25,26] This may be explained by the fact that those studies were hospital-based.

Antidepressant drug use was identified in 21 (1.1%) of 1,876 people without PES or glaucoma and in 3 (4.1%) of 74 patients with PES but without glaucoma, which was a statistically significant difference (p=0.024).

There is only one study in the literature showing an association between PES and depression, and it was conducted in patients with PXG. Cumurcu et al.[21] evaluated the prevalence of depression in 41 PXG patients, 32 POAG patients, and 40 control groups. Based on findings from other researchers indicating that depression was common in chronic disease and reasoning that glaucoma was a chronic disease, they expected depression rates to be higher in both PXG and POAG patients; however, only the PXG group showed a significantly higher prevalence of depression compared to the control group.[27] The higher prevalence of depression in the PXG group suggested that the vascular damage involved in the pathogenesis of depression might be associated with pseudoexfoliation, supporting the vascular depression hypothesis.[27,28] Unlike the study by Cumurcu et al.,[21] we excluded patients with glaucoma to include subjects with PES only. Numerous studies have shown that depression is more common in patients with CAD, diabetes, and HT.[29,30] Of the 6 participants with PES and psychiatric disease identified in our study, 4 had concomitant diabetes, HT, or CAD; considering the vascular etiology of depression, this may have increased antidepressant use in these patients. The presence of multiple chronic comorbidities may have led to depression in these individuals.

Oxidative damage and inflammation caused by free radicals was shown to have a role in the pathogenesis of PES.[5,6,7] Various studies have also reported that oxidative stress and inflammation may be involved in the pathogenesis of depression.[31,32] Inflammation induced by the accumulation of pseudoexfoliative material in the brain may trigger depression and increase antidepressant drug use in PES patients.

Moreover, ischemic heart disease, history of angioplasty, HT, and hearing loss were more common in the PES group than in controls. The higher prevalence of other diseases, even if not statistically significant, may be a factor contributing to antidepressant drug use. Loss of health and the limitations imposed by chronic diseases cause the higher incidence of depression with these diseases.[33] Various studies have shown that

Table 1. Age and sex distribution of participants with and without pseudoexfoliation syndrome

	n	%	Mean age (years) sex	Mean age (years) general
Female		53	67.3±10.7	
PES (+) (n=100)				69.1±9.9
Male	47	47	71.1±8.7	
Female	1025	53.7	57.7±10.4	
PES (-) (n=1909)				59.2±10.9
Male	884	46.3	60.9±11.0	

PES: Pseudoexfoliation syndrome

Table 2. Comparison of antidepressant use in participants with and without pseudoexfoliation syndrome

	PES (+), n (%)	PES (-), n (%)	p
Antidepressant drug use	3 (4.1)	21 (1.1)	p=0.024

PES: Pseudoexfoliation syndrome

Table 3. The distribution of participants with and without pseudoexfoliation syndrome diagnosed with depression and using antidepressant drugs

		PES (+), (n=4)	PES (-), (n=22)
SSRI	Escitalopram	2	9
	Citalopram	-	1
	Sertraline	1	6
	Paroxetine	-	1
SNRI	Venlafaxine	1	5

PES: Pseudoexfoliation syndrome, SSRI: Selective serotonin reuptake inhibitor, SNRI: Serotonin-norepinephrine reuptake inhibitor

Table 4. Comparison of systemic drug use in participants with and without pseudoexfoliation syndrome

	PES (+), n (%)	PES (-), n (%)	p
Antihypertensive drug	48 (48)	626 (32.8)	p<0.001
Cardiac drug	22 (22)	210 (11.0)	p=0.001
Antidiabetic drug	25 (25)	483 (25.3)	p>0.05
Hypercholesterolemia drug	3 (3)	57 (3.0)	p>0.05
Neurologic drug	8 (8)	92 (6.1)	p>0.05
Antithyroid drug	7 (7)	120 (6.3)	p>0.05
Antirheumatic drug	2 (2)	37 (1.9)	p>0.05
Asthma/COPD medication	6 (6)	69 (3.6)	p>0.05
Gastrointestinal disease medication	6 (6)	41 (2.7)	p>0.05
Osteoporosis medication	2 (2)	28 (1.5)	p>0.05
Prostate disease medication	2 (2)	32 (1.7)	p>0.05

PES: Pseudoexfoliation syndrome, COPD: Chronic obstructive pulmonary disease

depression is more common in patients with CAD, diabetes, asthma, and cancer.[34,35,36,37]

Of the 100 PES patients in our study, 48% had HT and 17% had ischemic heart disease; consistent with the literature, these rates were significantly higher when compared with patients without PES ($p<0.001$). Previous studies have demonstrated the relationship between PES and systemic diseases such as HT, CAD, heart attack, peripheral vascular diseases, ischemic brain diseases, stroke, and Alzheimer's disease.[14,15,16,17,18,19,20] In a recent study, 62% of 260 patients who presented for cataract surgery had cardiovascular diseases, 46.5% with HT and 19.7% with ischemic heart disease.[38] Furthermore, a significant relationship has been reported between PES and sensorineural hearing loss.[39,40]

Study Limitations

Limitations of our study are that we did not perform brain imaging in PES patients using antidepressant drugs to rule out a central etiology of depression, and we did not evaluate for family history of depression.

Conclusion

The higher prevalence of antidepressant drug use among patients with PES illustrates the need for further research to determine the relationship between PES and depression.

Ethics

Ethics Committee Approval: Eskişehir Osmangazi University (7 February 2013, decision no: 06).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Nilgün Yıldırım, Design: Eray Atalay, Data Collection or Processing: Erdoğan Yaşar, Analysis or Interpretation: Nilgün Yıldırım, Literature Search: Erdoğan Yaşar, Writing: Erdoğan Yaşar.

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Original Article

Evaluation of the Effect of Body Position on Intraocular Pressure Measured with Rebound Tonometer

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Abstract

Objectives: It is important to determine variables that influence intraocular pressure (IOP) measurement. This study aimed to evaluate the effect of body position on IOP.

Materials and Methods: The study included 52 right eyes of 52 patients who presented to the ophthalmology department of our hospital and had no ocular disease except refractive errors. IOP was measured with an Icare PRO tonometer while patients were in sitting, standing, and supine positions, with intervals of 10 minutes between the positions. Correlations between the results were evaluated using Spearman's correlation analysis and Wilcoxon tests.

Results: Thirty-six of the 52 patients were female, 16 were male. Mean age was 31.65±6.30 (23-47) years. Mean IOP values in the sitting, standing, and lying positions were 17.76±3.41 (12.70-25.60) mmHg, 17.10±3.27 (11.50-25.20) mmHg, and 18.46±4.67 (10.50-29.40) mmHg, respectively. There were no statistically significant differences between measurements taken in the different positions ($p=0.112$, $p=0.472$, $p=0.071$). We observed that there was no relationship between age and body position ($p>0.45$, $p>0.79$, $p>0.77$) or between gender and position ($p>0.59$, $p>0.69$, $p>0.54$).

Conclusion: Gender and age had no effect on IOP measured in different body positions. There were also no significant differences between IOP values measured in the different positions. Therefore, we believe the portable Icare PRO tonometer can be used for patients who are confined to bed and will provide IOP measurements that are concordant with values obtained while sitting.

Keywords: Intraocular pressure, body position, tonometer

Introduction

Glaucoma is one of the causes of substantial visual loss due to optic nerve injury. High intraocular pressure (IOP) is the most important risk factor. However, IOP is dynamic and can be affected by many factors. Pronounced changes in IOP in horizontal body position have been demonstrated in previous studies, and people spend one third of their lives lying down.[1,2,3,4,5,6]

Positional changes in IOP may be important in the development and course of glaucoma. Previous studies have also demonstrated wide variation in the difference between IOP values obtained in supine position and sitting position. This difference varies between 0.3 mmHg and 5.6 mmHg in studies evaluating healthy individuals and patients with glaucoma.[7,8,9,10,11,12,13,14,15,16,17]

The physiology of postural changes in IOP is not fully understood. Understanding IOP changes related to body position may be important in order to understand the development and course of glaucoma, determine variations in IOP measurements obtained in clinical follow-up, and provide more standardized follow-up. Furthermore, if the nature of these effects is better understood, glaucoma patients can be advised about what

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situations they should avoid in their daily lives or which may benefit them.

In this study, we measured IOP in healthy individuals in sitting, standing, and supine position and evaluated differences in IOP between these positions.

Materials and Methods

The study was carried out in accordance with the principles of clinical research set forth in the Declaration of Helsinki and was approved by the Ethics Committee of Manisa Celal Bayar University Faculty of Medicine. Fifty-two right eyes of 52 individuals who presented to the ophthalmology department of the Manisa Celal Bayar University Hafsa Sultan Faculty of Medicine with refractive errors not exceeding -4.00 and +2.00 were included in the study. Patients using systemic or topical medication and those with ocular surface disease, uveitis, glaucoma, retinal detachment, ocular infection, and strabismus were not included. A detailed ophthalmologic examination was performed before the study to identify individuals who met these criteria. In addition, the nature of the study was explained verbally to each participant and informed consent was obtained from all participants before the study. Participants were instructed to sleep normally the night before and to abstain from excessive caffeine intake on the day of the study.

The Icare PRO rebound tonometer (Icare; Tiolat Oy, Helsinki, Finland) was used in this study. Subjects were seated for 10 minutes, after which 6 serial IOP measurements were taken in quick succession from their right eye with the Icare PRO tonometer while they remained in sitting position. The average of these 6 measurements was used. The subjects were then asked to stand for 10 minutes, after which 6 serial IOP measurements and their average value were obtained as before. Finally, the patients laid in supine position on the clinic stretcher with no pillow for 10 minutes, after which the same IOP measurement procedure was repeated. Subjects were encouraged to relax in order to avoid actions that would increase pressure on the eyelids or globe during measurements. Based on the color-coded measurement reliability system in the Icare PRO tonometer, we only used average values that were green, indicating low variability and high reliability. The Icare PRO includes an automatic system that compares 6 manual measurements, evaluating variation between them and calculating an average. Green indicates lowest variability and highest reliability, yellow indicates moderate variability and reliability, and red indicates high variability and low reliability.[2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18]

Statistical Analysis

Using the SPSS program, normality of the sample set was evaluated and the non-parametric Spearman's correlation test and Wilcoxon test were used to statistically evaluate relationships between the participants' age and sex, respectively, and the different body positions. P values <0.05 were considered statistically significant.

Results

Of the 52 participants, 36 were female and 16 were male; their mean age was 31.65±6.30 (23-47) years. Table 1 shows that the sample set was not normally distributed. Table 2 shows the mean IOP values obtained in sitting, standing, and supine positions and statistical comparisons between these values using Wilcoxon test.

A p value >0.05 in this test of normality indicated that the group was not distributed normally. Therefore, non-parametric tests were used in all further statistical analyses.

There were no statistically significant differences in IOP values obtained in sitting when compared with values obtained in standing and supine position (p=0.112, p=0.472). There was also no significant difference in the comparison of standing and supine position (p=0.071).

The relationship between the participants' age distribution and IOP in different body positions was examined using Spearman's correlation test (Table 3) and the relationship between sex and IOP in different body positions was examined using the Wilcoxon test (Table 4).

No relationship was observed between age and IOP measured in sitting, standing, and supine positions (p=0.45, p=0.79, p=0.77). There was a positive correlation between age and IOP in sitting and standing position, while a negative correlation was observed in supine position. Relationships between sex and IOP measured in sitting, standing, and supine positions were not statistically significant according to the results of the Wilcoxon test (p=0.59, p=0.69, p=0.54).

Discussion

Changes in IOP occurring with changes in body position have been evaluated in numerous studies over the years, with emphasis that this issue may be important for patients with glaucoma. Previous studies have shown that IOP differs significantly between sitting and supine position and that IOP is higher in supine position compared to sitting position. Furthermore, these studies reported that the difference in IOP between sitting and

Table 1. Normality test

Kolmogorov-Smirnov test	
	p
Female	0.001
Male	0.066

Table 2. Statistical comparison of mean intraocular pressure values measured in different body positions

Body positions	**Mean intraocular pressure (mmHg)**	**p**
Sitting	17.76±3.41 (12.70-25.60)	Vs. standing p=0.112; vs. supine p=0.472
Standing	17.10±3.27 (11.50-25.20)	Vs. supine p=0.071
Supine	18.46±4.67 (10.50-29.40)	

Table 3. Relationship between age and intraocular pressures measured in sitting, standing, and supine positions

	Sitting	Standing	Supine
Vs. age p value	p=0.488	p=0.793	p=0.778
Correlation coefficient with age	0.098	0.037	-0.040

Table 4. Relationship between sex and intraocular pressures measured in sitting, standing, and supine positions

Body positions	Vs. sex p value
Sitting	p=0.597
Standing	p=0.697
Supine	p=0.541

supine position was more pronounced in glaucoma patients. The magnitude of this difference is 0.3-5.6 mmHg in healthy individuals and patients with glaucoma.[1,7,8,9,10,11,12,13,14,15,16,17]

The physiology of posture-induced changes in IOP has not been fully elucidated. However, in another study involving 24-hour observation, it was emphasized that IOP has a circadian rhythm. The authors reported a change of 4.5-20 mmHg between IOP values taken at night in supine position and in the day in sitting position. This indicates that IOP measurements in glaucoma patients should be performed at similar times of day and also suggests that IOP spikes that may accelerate glaucoma progression could go undetected and unnoticed by clinicians.[2,19]

Axial length, which is believed to be a factor in the physiology of IOP change, has also been evaluated in some studies. The increase in intraocular pressure when moving from sitting to supine position was found to be greater in patients with short axial length and smaller increases were observed in patients with myopic defocus greater than -4.00 diopters.[1,20,21]

In numerous studies, the increase in episcleral venous pressure (EVP) that occurs when lying down was proposed as an explanation of this change in IOP. However, these studies were unable to show an exact correlation between EVP increase and expected IOP increase or clearly demonstrate whether IOP increase was a result of the EVP increase or other factors.[22,23,24,25]

Different methods of evaluating IOP changes according to body position have been described in the literature. In healthy subjects, the increase in IOP between sitting and supine position was reported as 1.8 mmHg using Perkins applanation tonometer, 2.5-3.9 mmHg with pneumotonometer, 1.2 mmHg with Tono-Pen, and 4.1 mmHg with Goldman applanation tonometry.[1,26,27,28,29] Mosaed et al.[30] reported relatively small postural change in IOP in healthy young adults and elderly individuals with healthy eyes, while another study reported that postural IOP changes in these two populations were nonsignificant.[31]

Although our study did not yield any findings that support previous studies, we can say that changes in IOP are not related to body position. Because our study included only healthy young adults, the same results may not be obtained in elderly individuals or glaucoma patients. Our investigation focused on the relationship between IOP and body position, and we observed a difference of 0.7 mmHg between sitting and supine positions. A limitation of our study is that we did not control for systemic parameters such as blood pressure, heart rate, and central venous pressure.

Our results indicated that there was no statistically significant difference in IOP measured in sitting and supine position with the Icare PRO tonometer. Therefore, we believe the Icare PRO tonometer may be appropriate for IOP monitoring in glaucoma patients who are confined to bed. The other main finding of our study is that differences in IOP values when sitting, standing, and in supine position are independent of sex and age.

Study Limitations

In our study, we used the Icare PRO tonometer to measure IOP in randomly selected healthy individuals in a specific order (sitting, then standing, then supine). This was important in terms of standardizing the measurement process between participants. However, the relatively small sample and inclusion of only healthy individuals were among the limitations of this study.

Conclusion

A more comprehensive study is needed to understand how IOP changes with respect to position and time of day and to determine whether these factors affect glaucoma. These studies will help develop recommendations for glaucoma patients with comorbidities on how to optimize their living conditions.

Ethics

Ethics Committee Approval: Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee-20/12/2017/20.478.486.

Informed Consent: In addition, the nature of the study was explained verbally to each participant and informed consent was obtained from all participants before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Hüseyin Mayalı, Beyza Tekin, Concept: Hüseyin Mayalı, Beyza Tekin, Özcan Rasim Kayıkçıoğlu, Süleyman Sami İlker, Design: Beyza Tekin, Özcan Rasim Kayıkçıoğlu, Süleyman Sami İlker, Emin Kurt, Data Collection or Processing: Hüseyin Mayalı, Beyza Tekin, Analysis or Interpretation: Özcan Rasim Kayıkçıoğlu, Süleyman Sami İlker, Emin Kurt, Literature Search: Hüseyin Mayalı, Beyza Tekin, Süleyman Sami İlker, Emin Kurt, Writing: Hüseyin Mayalı, Beyza Tekin.

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Original Article

Etiological and Clinical Characteristics of HLA-B27-associated Uveitis in a Tertiary Referral Center

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Abstract

Objectives: To investigate the demographic, etiologic, and clinical features of HLA-B27-associated uveitis.

Materials and Methods: The clinical records of 91 patients diagnosed with HLA-B27-associated uveitis at the Ulucanlar Eye Training and Research Hospital between the years of 2005 and 2016 were reviewed. Each patient's presenting complaints, best-corrected visual acuities in first and last visits, biomicroscopic and fundoscopic examination findings, frequency and seasonal distribution of attacks, and demographic data such as age and sex were noted. Therapeutic approaches, duration of follow-up, and complications were analyzed.

Results: A total of 91 patients (179 eyes) aged 19-82 years (mean age 46.52±13.06 years) were included. Forty-three patients (47.3%) were female and 48 (52.7%) were male. Bilateral involvement was observed in 44 (48.4%) and unilateral involvement was observed in 47 (51.6%) patients. The most frequent complaint was redness (67%), followed by decreased and/or blurred vision (50.5%). The mean follow-up time was 38.2 months (range, 1-245 months). Anterior uveitis was most common anatomical subtype, seen in 86 (94.5%) of the patients. Mean number of attacks was 1.93±1.45 per patient-year and a significantly higher number of uveitis attacks (47%) occurred in winter. Twenty-four patients (26.3%) were diagnosed with ankylosing spondylitis. Fibrinous uveitis was detected in 36 patients (39.5%). Posterior synechia developed in 41 (22.9%) and hypopyon developed in 7 (3.9%) eyes. The most common complications were cataract (n=12, 6.7%) and ocular hypertension (n=15, 8.3%).

Conclusion: Ninety-one (6.3%) of the 1422 patients followed in our uvea clinic were diagnosed with HLA-B27-associated uveitis. HLA-B27-associated uveitis is characterized by acute, recurring sudden-onset iridocyclitis with a moderate to severe amount of fibrin and cells in the anterior chamber, and is easily treatable. Visual prognosis is good despite the complications.

Keywords: HLA-B27, uveitis, ankylosing spondylitis, demography, etiology

Introduction

Uveitis, which is defined as intraocular inflammation, predominantly affects the working-age population (20 to 50 years old) and leads to substantial individual and socio-economic burdens.[1] Anatomic location of inflammation, disease course, and the presence of comorbid infectious or systemic disease should be considered when evaluating a patient with uveitis.[2]

The most common form is anterior uveitis and the most common subtype is acute anterior uveitis (AAU).[3] HLA-B27-associated uveitis is the most common cause of anterior uveitis overall and of anterior uveitis with hypopyon in particular.[4,5,6] The diagnosis of HLA-B27-associated AAU is based on clinical findings and positive HLA-B27 antigen test after ruling out other infectious or inflammatory diseases. In spite of ongoing research, the pathogenesis of HLA-B27-associated uveitis is not fully understood. In addition, patients with HLA-B27-associated uveitis vary in terms of their clinical features, response to treatment, and systemic comorbidities.[7]

The aim of this study was to identify the clinical spectrum and related systemic diseases in HLA-B27-associated uveitis by investigating the etiological and clinical features of patients who presented to a tertiary eye care center and were diagnosed with HLA-B27-associated uveitis.

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Materials and Methods

The clinical records of 91 patients who were diagnosed with HLA-B27-associated uveitis and followed for at least 6 months in the Ulucanlar Eye Hospital between the years 2005 and 2016 were evaluated retrospectively. The study protocol was approved by the ethics committee and the study was performed according to the Declaration of Helsinki. Written informed consent was obtained from each participant.

In all cases, the presence of Behçet's disease, viral anterior uveitis demonstrated with clinical findings and laboratory tests when necessary, syphilis (which can mimic any clinical condition), and sarcoidosis and tuberculosis etiologies in clinically suspicious cases were ruled out. All patients were questioned about backache and morning stiffness, and rheumatology consultation was requested to evaluate for the potential comorbidities ankylosing spondylitis (AS) and other spondyloarthropathies, as well as to test for HLA-B27 positivity. Seven patients who were followed for less than 6 months were excluded.

The patients were analyzed in terms of demographic data such as sex and age at uveitis onset, presenting complaints, best corrected visual acuity (BCVA) at initial and final visits as measured by Snellen scale, intraocular pressure (IOP) measured using a noncontact tonometer, and detailed ophthalmological examination findings including slit-lamp and fundus examination findings.

Ocular involvement was classified as recurrent in the same eye (unilateral), recurrent in both eyes at different times (bilateral alternating), or recurrent in both eyes at the same time (bilateral simultaneous). During acute episodes, the IOP values in both eyes were compared. Patients with posterior synechia, hypopyon, and/or fibrinous reaction in the anterior chamber were recorded separately. The frequency and seasonal distribution of uveitis attacks were noted. Follow-up time, systemic comorbidities, therapeutic approaches, complications, and surgical procedures were also analyzed.

IOP over 21 mmHg in two examinations was defined as ocular hypertension in the absence of detectable visual field defect and as secondary glaucoma when accompanied by visual field loss. Complicated cataract induced by uveitis was defined as posterior subcapsular opacity that developed subsequently in the lens.

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences version 22.0 software (SPSS Inc., Chicago, IL, USA). Mean values, percentages, and chi-square test were used for statistical analyses. P value less than 0.05 was considered significant.

Results

Ninety-one of 98 patients aged 19-82 years (mean 46.52±13.06 years) were included in the study. Demographic and clinical features of the patients are presented in Table 1. Forty-three (47.3%) of the patients were women and 48 (52.7%) were men. Patients diagnosed with HLA-B27-associated uveitis comprised 6.3% (91/1422) of the patients under follow-up in our uvea unit.

Presenting symptoms of the patients are shown in Table 2. The most common presenting symptom was redness (67%), followed by reduced visual acuity (50.5%). Mean follow-up time was 38.2 (6-245) months. Forty-four (48.4%) of the patients had bilateral and 47 (51.6%) had unilateral involvement. Fourteen (31.8%) of the 44 patients with bilateral involvement had simultaneous episodes, while the remaining (68.2%) had bilateral alternating involvement. In terms of anatomic location, anterior uveitis was most common, detected in 86 (94.5%) of the patients. Of the remaining 5 patients, 3 had intermediate uveitis and 2 had panuveitis.

Of the 135 eyes with acute uveitis episodes, there was a significant difference between mean initial BCVA (0.2±0.37) and mean final BCVA (0.11±0.25) converted to LogMAR (logarithm of the minimum angle of resolution) ($p<0.0001$). Clinical findings included posterior synechia in 41 patients (22.9%) (Figure 1), presence of fibrin during acute episodes in 36 patients (39.5%), (Figure 2) and hypopyon in 7 patients (3.9%) (Figure 3). Posterior synechia was present in 35 eyes (85.4%) at presentation and developed during follow-up in 6 eyes (14.6%). During acute episodes, IOP in the uveitic eye was ≥5 mmHg lower than in the nonuveitic eye in 17 (18.6%) patients and ≥5 mmHg higher in 15 (16.4%) patients. In terms of posterior segment findings, macular edema was observed in 1 patient.

Table 1. Demographic and clinical characteristics of the patients

Age (years)	
Mean	46.5
Min-Max	19-82
Sex	
Female	43 (47.3%)
Male	48 (52.7%)
Laterality	
Unilateral	47 (51.6%)
Bilateral alternating	30 (33.0%)
Bilateral simultaneous	14 (15.4%)
Anatomic location	
Anterior uveitis	86 (94.5%)
Intermediate uveitis	3 (3.3%)
Posterior uveitis	0 (0%)
Panuveitis	2 (2.2%)

Table 2. Patients' symptoms at presentation

Presenting complaint	n (%)
Redness	61 (67%)
Reduced visual acuity/blurred vision	46 (50.5%)
Photophobia	25 (27.4%)
Pain	22 (10.9%)

The mean number of acute episodes per year was 1.93±1.45 and all patients had at least 1 attack during follow-up. Evaluation of the seasonal distribution of attacks showed that they occurred most often in the winter months (47%), followed by summer (27.3%), spring (16.2%), and autumn (9.5%).

With regard to medical treatment, acute episodes were treated in all patients with a topical steroid and cycloplegic agent at appropriate doses based on the severity of inflammation. In addition, 23 eyes (12.8%) received subconjunctival injection for severe anterior segment inflammation, 1 eye (0.6%) received sub-Tenon's injection for macular edema, and 9 eyes (5.0%) were treated with topical antiglaucomatous therapy due to ocular hypertension. Twenty-nine patients (31.8%) also received oral indomethacin 2 or 3 times daily depending on severity of inflammation. A total of 6 (6.6%) patients were given oral steroid therapy, 5 (5.5%) for severe ocular inflammation and 1 (1.1%) for macular edema. All patients diagnosed with AS were taking sulfasalazine (Salazopyrin). The rheumatology department prescribed oral steroid therapy to 2 patients (2.2%), methotrexate to 3 (3.3%), cyclosporine to 1 (1.1%), and infliximab to 1 patient (1.1%).

Systemic comorbidities included AS in 24 patients (26.3%), undifferentiated spondyloarthropathy in 8 patients, rheumatoid arthritis in 2, psoriasis in 1, and Crohn's disease in 1 patient. Fibrinous reaction was not associated with presence of AS (p=0.291) (Table 3). Prevalence rates of ocular complications are presented in Table 4. The most common complications during follow-up were complicated cataract (n=12, 6.7%) and ocular hypertension (n=15, 8.3%). Eight eyes (4.4%) underwent phacoemulsification and intraocular lens implantation, while 1 (0.56%) underwent trabeculectomy due to secondary glaucoma.

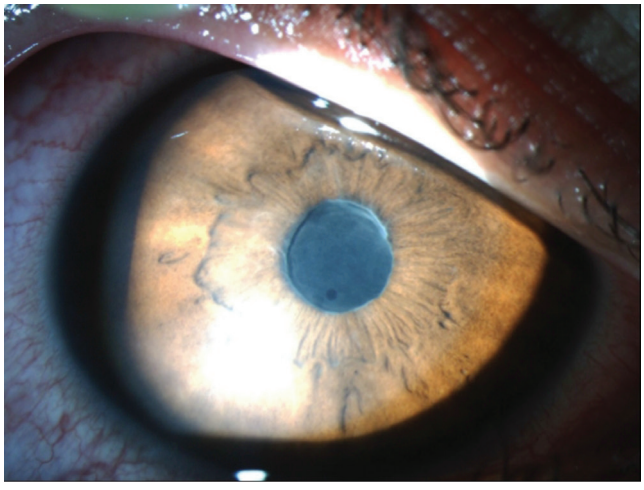

Figure 1. Anterior segment photograph of a patient with HLA-B27-associated uveitis showing broad-based posterior synechia

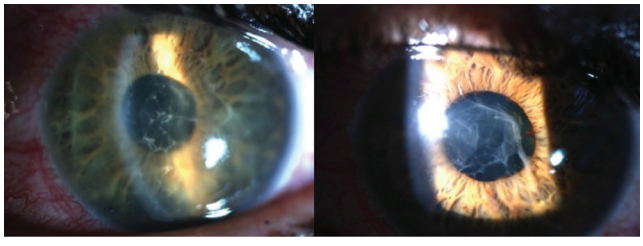

Figure 2. Anterior segment photograph of a patient with HLA-B27-associated uveitis showing fibrinous uveitis (left) and regression of the fibrinous reaction after 3 days of topical therapy (right)

Discussion

The relationship between HLA-B27 positivity and inflammatory diseases such as uveitis, AS, reactive arthritis, ulcerative colitis, and psoriasis was first identified in 1973.[8,9,10,11] There are substantial global differences in the prevalence of HLA-B27 antigen. These differences also explain observations of different global patterns of uveitis. In their publication on the demographic and clinical properties of uveitis in Turkey, Yalçındağ et al.[12] reported the prevalence of HLA-B27 antigen in the Turkish population as 6.8% and that HLA-B27-associated

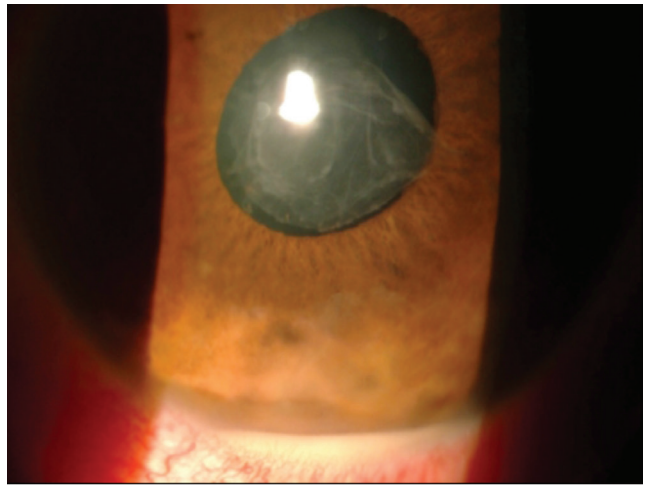

Figure 3. Anterior segment photograph of a patient with HLA-B27-associated uveitis showing hypopyon

Table 3. Relationship between ankylosing spondylitis and fibrinous reaction

	Fibrinous reaction (+)	Fibrinous reaction (-)
Ankylosing spondylitis (+)	10	14
Ankylosing spondylitis (-)	20	47

Table 4. Structural ocular complications in HLA-B27-associated uveitis

Complication	n (%)
Complicated cataract	12 (6.7%)
High intraocular pressure (>21 mmHg)	15 (8.3%)
Posterior synechia	41 (22.9%)
Present at presentation	35 (85.4%)
Developed during follow-up	6 (14.6%)
Macular edema	1 (1.1%)

uveitis accounted for 3.9% of all cases of uveitis. In their epidemiological study of uveitis, Özdal et al.[13] determined that HLA-B27-associated uveitis comprised 4.6% of uveitis cases. The proportion of HLA-B27-associated uveitis in the present study was 6.3% of all uveitis cases. The lower rates reported in previous studies may be due to the exclusion of uveitis associated with AS and other spondyloarthropathies.

HLA-B27-associated uveitis is characterized by symptomatic unilateral anterior uveitis with sudden onset and limited duration. Our study also showed that patients with HLA-B27-associated uveitis were symptomatic at time of presentation, that anterior uveitis was the most common type based on anatomic location, and most patients exhibited unilateral involvement. The majority of studies in the literature concerning sex distribution have reported male predominance. In the Turkish population, Kazokoglu et al.[13] reported a slight female predominance, whereas Yalçındağ et al.[12] and Tuncer et al.[14] observed male predominance, consistent with our study.

In active periods of HLA-B27-associated uveitis, IOP is expected to be lower due to ciliary body inflammation and reduced aqueous production. van der Veer et al.[15] reported 5 patients who developed hypotony and serous retinal detachment secondary to HLA-B27-associated anterior uveitis, while Roe et al.[16] reported 1 case with hypotony maculopathy. However, IOP may be high due to trabeculitis, accumulation of inflammatory cells and waste in the trabecular network, and/or steroid use. In the present study, IOP was lower in the eye with acute uveitis in 18.6% and higher in 16.4% of the patients.

In the literature related to posterior segment involvement in HLA-B27-associated uveitis, Rothova et al.[17] reported detecting no posterior segment involvement in 153 patients with seronegative spondyloarthropathies and/or HLA-B27-associated uveitis, and Mapstone and Woodrow[18] reported involvement in only 2 (3.9%) of 51 patients. In a cohort study of 166 patients with HLA-B27-associated uveitis, Rodriguez et al.[19] described 29 patients (17.4%) with posterior segment inflammatory findings. They attributed this high rate to the fact as a tertiary health center, referred cases were particularly difficult and complex. In our department, which is in one of the largest tertiary health centers in Turkey, panuveitis accompanied by vitreous haze and retinal vasculitis was observed in 2 patients and macular edema with severe anterior segment reaction was detected in only 1 patient.

A study examining the Turkish patient population in terms of the clinical features of HLA-B27 positive and negative AAU patients showed that 7% of HLA-B27 positive AAU cases had concurrent bilateral AAU, whereas this proportion was higher in our study (31.8%).[14] The prevalence of AS in HLA-B27-associated AAU was shown to be 22-39% in several studies.[20,21,22] Tuncer et al.[14] determined this rate to be 43% in their study on the Turkish population, and we found this rate to be 26% in our series. Half of HLA-B27 positive AAU patients can develop uveitis before the onset of spondylitis, with an average of 3 years between uveitis and spondylitis onset.[22,23,24] Our findings also support the importance of taking a detailed history and conducting a thorough investigation for potential systemic comorbidities in all patients with HLA-B27-associated uveitis. There are publications showing that HLA-B27 positive patients with systemic disease have a higher probability of recurrent uveitis episodes than those without systemic symptoms.[20,25] However, Gehlen et al.[26] reported that uveitic activity may not always be related to the activity of systemic HLA-B27-associated disease. In the present study, we observed no statistically significant difference in attack frequency between patients with and without systemic disease ($p>0.05$).

Inflammation in HLA-B27-associated uveitis generally responds well to topical therapy. However, patients sometimes present with hypopyon, fibrinous reaction in the anterior chamber, and pupillary seclusion; response to topical therapy is insufficient in these cases. HLA-B27 antigen positivity was detected by Power et al.[20] in 14.1% and by D'Alessandro et al.[27] in 14.5% of anterior uveitis patients presenting with hypopyon. In our series, hypopyon was observed in 3.4% of patients. The formation of fibrinous membrane in the absence of granulomatous precipitate was put forth as a classic presentation of HLA-B27-associated anterior uveitis.[18] However, Huhtinen and Karma[28] reported that fibrinous reaction was not more frequent in HLA-B27 positive unilateral AAU cases (43%) than in idiopathic HLA-B27 negative unilateral AAU cases (55%). Tuncer et al.[16] observed fibrinous reaction in 39% of HLA-B27 positive uveitis patients in the Turkish population, and this rate was 39.5% in our series.

There are studies in the literature analyzing changes in the seasonal distribution of AAU attacks.[30,31,32,33] Two of these studies evaluated the effect of HLA-B27 positivity on the seasonal distribution of AAU attacks, but their results were conflicting.[30,31] Chung et al.[31] evaluated only HLA-B27 positive AAU cases and found that recurrence was more likely in December through March (winter). In a population-based study investigating monthly variations in AAU cases, a statistically significant increase in the number of AAU attacks was detected in December in two consecutive years. Comparison of HLA-B27 positive and negative AAU cases revealed no statistically significant difference in monthly distribution between the two groups, but attacks tended to recur more in late winter in HLA-B27 positive patients.[32] We also observed in the present study that attacks were more common in the winter months. This difference in the seasonal distribution of AAU attacks suggests that weather conditions may be a factor.

Conclusion

In conclusion, our study suggests that HLA-B27-associated uveitis is characterized by anterior segment inflammation that has limited duration and shows unilateral or alternating bilateral involvement, and that uveitis may coexist with systemic diseases, particularly AS. Despite the development of complications, visual prognosis is good with appropriate treatment to control inflammation.

Ethics

Ethics Committee Approval: Ankara Numune Training and Research Hospital Clinical Research Ethics Committee E-15-670

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Müge Pınar Çakar Özdal, Concept: Müge Pınar Çakar Özdal, Design: Müge Pınar Çakar Özdal, Data Collection or Processing: Merve İnanç, Mert Şimşek, Analysis or Interpretation: Müge Pınar Çakar Özdal, Merve İnanç, Literature Search: Merve İnanç, Writing: Merve İnanç.

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Original Article

First-Year Outcomes of Cataract Surgery Combined with Intravitreal Ranibizumab Injection in Wet Age-Related Macular Degeneration

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Abstract

Objectives: To compare the first-year results of patients with active neovascular age-related macular degeneration (nAMD) under intravitreal ranibizumab (IVR) treatment who did and did not undergo cataract surgery.

Materials and Methods: The records of 72 patients with active nAMD were reviewed retrospectively. Group 1 consisted of 23 patients who underwent uncomplicated cataract surgery and continued with IVR treatment and group 2 consisted of 49 patients without cataract who received only IVR treatment. The groups were compared according to pretreatment and first year best spectacle-corrected visual acuity (BCVA), central foveal thickness (CFT), number of injections, and nAMD activity (presence of subretinal or intraretinal fluid). Logarithm of minimum angle of resolution (LogMAR) was used for the determination of visual acuity. Activity findings were evaluated with optical coherence tomography.

Results: Pretreatment BCVA was 0.94±0.21 in group 1 and 0.77±0.36 in group 2 (p=0.041). At the end of the first year, BCVA was 0.48±0.35 in group 1 and 0.49±0.33 in group 2 (p=0.902). BCVA change was 0.46±0.29 in group 1 and 0.28±0.31 in group 2 (p=0.026). Pretreatment CFT was 305±146 µm in group 1 and 340±120 µm in group 2 (p=0.292). At the end of the first year, CFT was 246±110 µm and 245±82 µm in group 2 (p=0.977). CFT change was 59±45 µm in group 1 and 92±97 µm in group 2 (p=0.135). Mean number of injections over 1 year was 6.2±1.9 in group 1 and 5.7±1.8 in group 2 (p=0.271). At the end of the first year, subretinal fluid was observed in 3 patients in group 1 (13%) and 5 patients in group 2 (10.2%) (p=0.721) and intraretinal fluid was present in 3 patients in group 1 (13%) and 4 patients in group 2 (8.2%) (p=0.515).

Conclusion: Cataract surgery combined with IVR treatment yielded significant visual gain in patients with active nAMD. Anatomic results suggest that cataract surgery does not worsen nAMD.

Keywords: Neovascular age-related macular degeneration, ranibizumab, cataract surgery

Introduction

Age-related macular degeneration (AMD) and cataract are the main causes of vision loss in the elderly population.[1,2] With longer average life expectancy in developed countries, the incidence rates of AMD and cataract are increasing. Today, treatment of neovascular AMD with anti-vascular endothelial growth factors (anti-VEGFs) stabilizes or increases vision in most patients.[3,4] The timing of cataract surgery is important in AMD patients; there is still debate regarding the effect of cataract

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surgery on AMD progression. Although some authors have reported that cataract surgery encourages AMD progression, others studies showed that cataract surgery had no effect on the progression of AMD.[5,6,7,8,9]

The aim of this study was to evaluate and compare 1-year visual and anatomic outcomes in patients with active neovascular AMD treated with intravitreal anti-VEGF therapy who did and did not undergo cataract surgery.

Materials and Methods

We retrospectively evaluated the records of patients with active neovascular AMD with or without cataract who received intravitreal ranibizumab (IVR) therapy (0.5 mg/0.05 mL) with or without uneventful phacoemulsification surgery in 2016-2017. Ethical approval for the study was obtained from the Ethics Committee of Muğla Sıtkı Koçman University Medical Faculty and the study was conducted in accordance with the Declaration of Helsinki. Consent forms were obtained from all patients before each intraocular injection and cataract surgery.

The patients were divided into two groups, those with nAMD + cataract who underwent both cataract surgery and IVR therapy (group 1) and phakic patients with nAMD but no cataract who underwent IVR therapy only (group 2). Age, sex, best corrected visual acuity (BCVA), complete ophthalmologic examination records, fundus fluorescein angiography (FA), and optical coherence tomography (OCT) measurements were recorded before treatment in both groups. All patients received 3 monthly injections of 0.5 mg IVR initially, after which IVR injections were repeated as needed. Repeat injections were given to patients with intraretinal and/or subretinal fluid in OCT. Patients who had no signs of disease activity and had not received IVR treatment for at least 3 months but showed activation at the last visit were included in the study. IVR injection and cataract surgery were combined in patients in group 1. Patients with visual loss associated with other retinal (retinal vascular pathologies) or corneal pathologies and patients with choroidal neovascularization not related to AMD were excluded from the study. All patients were followed monthly for 1 year. Visual and anatomic response at 1 year and total injection numbers were evaluated and compared between the groups. Pre- and post-treatment visual acuities were measured using Snellen chart and converted to LogMAR for statistical analysis. Central foveal thickness (CFT), presence of subretinal or intraretinal fluid (increase, decrease, or no change), and subfoveal choroidal thickness were used to evaluate and compare anatomic response.

Statistical Analysis

SPSS (version 22.0) statistical program was used to evaluate the study data. T-test and chi-square test were used in comparisons of continuous and categorical variables between the groups, respectively. $P<0.05$ was considered statistically significant.

Results

Seventy-two eyes of 72 patients were included in the study. Group 1 included 23 eyes and group 2 included 49 eyes. Mean age was 72.1±5.1 (64-85) years in group 1 and 74.3±6 (62-87) years in group 2 (p=0.151). Male:female ratios were 14:9 (60.9%/39.1%) in group 1 and 37:12 (75.5%/24.5%) in group 2 (p=0.203). The change from pre-treatment to 1-year BCVA was significantly greater in group 1 than in group 2 (Table 1). There was no significant difference between the groups in 1-year BCVA (Table 1). At 1 year, visual acuity was unchanged in 3 patients (13%) and decreased in 1 patient (4.3%) in group 1. In group 2, visual acuity was unchanged in 10 patients (20.4%) and decreased in 4 patients (8.2%). Change in CFT was 59±45 µm in group 1 and 92±97 µm in group 2 (p=0.135). Pre-treatment

Table 1. Visual and anatomic characteristics and comparison of injection numbers in age-related macular degeneration patients with cataract (group 1) and without cataract (group 2) before and after treatment

	Group 1		Group 2		p
	Mean ± SD	Minimum - maximum	Mean ± SD	Minimum - maximum	
Initial BCVA (LogMAR)	0.94±0.21	0.4-1.3	0.77±0.36	0.2-1.3	**0.041**
Final BCVA (LogMAR)	0.48±0.35	0.1-1.3	0.49±0.33	0-1.3	0.902
Δ BCVA (LogMAR)	0.46±0.29	(-) 0.3-0.9	0.28±0.31	(-) 0.3-1.1	**0.026**
Initial CFT (µm)	305±146	170-868	340±120	173-667	0.292
Final CFT (µm)	246±110	148-697	245±82	79-438	0.977
Δ CFT (µm)	59±45	21-208	92±97	0-406	0.135
Initial CCT (µm)	177±44	99-240	196±45	70-260	0.084
Final CCT (µm)	161±41	78-227	175±44	60-236	0.226
Δ CCT (µm)	15±13	0-40	21±10	7-47	**0.031**
Number of injections	6.2±1.9	3-9	5.7±1.8	3-9	0.271

BCVA: Best corrected visual acuity, CFT: Central foveal thickness, CCT: Central choroidal thickness, Δ: Change, SD: Standard deviation

Table 2. Comparison of rates of subretinal exudation and intraretinal cyst before and after treatment in age-related macular degeneration patients who had cataract surgery (group 1) and those without cataract (group 2)

	Group 1 (n=23)	%	Group 2 (n=49)	%	p
Subretinal exudation (Pre-treatment)	21	91.3	44	89.8	0.840
Subretinal exudation (at 1 year)	3	13	5	10.2	0.721
Intraretinal cyst (at 1 year)	3	13	4	8.2	0.515

and 1-year CFT values were similar (Table 1). Mean number of injections was 6.2±1.9 in group 1 and 5.7±1.8 in group 2 (p=0.271) (Table 1). The prevalence of subretinal exudation was similar in groups 1 and 2 before treatment (Table 2). At 1 year, subretinal exudation was detected in 3 patients (13%) in group 1 and 5 patients (10.2%) in group 2 (p=0.721) and intraretinal cyst was observed in 3 patients (13%) in group 1 and 4 patients (8.2%) in group 2 (p=0.515).

Discussion

Cataract and AMD are common in the elderly population and their coexistence can compound visual impairment in this age group. There is no consensus regarding what treatment will provide maximum visual acuity in such cases. It is clear that the visual gains achieved with ongoing AMD treatment will be obscured by the presence of cataract. However, there is still debate concerning the effect of cataract surgery timing on the progression of AMD. In earlier studies on this subject it was reported that progression to advanced AMD was more rapid after cataract surgery. In the Beaver Dam Eye study, patients with early dry AMD showed a higher rate of advanced AMD (geographic atrophy or exudative form) after cataract surgery.[10] Cugati et al.[11] reported that patients who underwent cataract surgery had a 3.4-fold higher risk of developing choroidal neovascularization. The Rotterdam study also suggested that geographic atrophy was more common after cataract surgery.[2] In a study of patients with bilateral symmetric early AMD, Pollack et al.[5] found that eyes subjected to extracapsular cataract extraction and intraocular lens implantation showed higher incidence of wet AMD compared to unoperated eyes (19.1% in operated eyes vs. 4.3% in unoperated eyes). The Blue Mountains Eye, Beaver Dam Eye, and other population-based studies conducted before the anti-VEGF era included patients with dry AMD. The conclusion reached in these earlier studies that cataract surgery has a negative effect on AMD progression may be related to several factors. The first is that these studies compared patients with dry AMD with healthy elderly individuals. Considering the natural course of the disease, higher rates of nAMD development can be expected in some patients compared to healthy individuals. Wang et al.[12] conducted a clinical study comparing fellow eyes of AMD patients and found that cataract surgery had no effect on progression, while the presence of early AMD was the most important risk factor for the development of advanced AMD. Other factors may include inadequate AMD diagnosis or staging due to lens opacity and the use of extracapsular cataract extraction instead of modern phacoemulsification surgery (due to the more sudden change in intraocular pressure and probably more severe postoperative inflammation compared to phacoemulsification). More recent studies have not detected any association between cataract surgery and AMD progression. The Age-Related Eye Disease Study 2 study demonstrated significantly increased visual acuity after surgery.[13] In a randomized controlled trial in which FA was performed before and 6 months after surgery, nAMD was observed in only 1 of 27 patients who underwent surgery and none of the 29 patients who did not have surgery.[14] There was also a significant increase in visual acuity in the operated group. Akıncı and Yalnız[15] showed that cataract surgery had no effect on AMD progression in their 15 patients.

Before the anti-VEGF era, cataract surgery was not recommended in patients with neovascular AMD. It was believed that the inflammation, blood-retinal barrier disruption, and intraocular pressure changes resulting from surgery would lead to decompensation in the fragile choroidal vessels, thus causing further leakage and hemorrhage. However, since the introduction of anti-VEGF therapy, the effectiveness of anti-VEGFs against choroidal neovascularization and the better control of intraocular pressure provided by phacoemulsification have allowed cataract surgery to be performed more safely. In studies reported in the literature, cataract surgery is performed in neovascular AMD patients receiving anti-VEGF therapy. In a study by Furino et al.,[17] 20 patients with active neovascular AMD and cataract underwent phacoemulsification with intravitreal bevacizumab administered at the end of surgery. The authors reported a significant increase in visual acuity and a significant decrease in central retinal thickness after 1 month. Tabandeh et al.[18] reported that cataract surgery improved visual acuity in patients receiving anti-VEGF therapy with no increase in reactivation during follow-up. In their retrospective controlled study, Saraf et al.[19] also determined that cataract surgery improved visual acuity and was not associated with worsening AMD. In addition, they reported greater retinal thickness in the operated eyes and stated that surgery in these eyes could cause a predisposition for cystoid macular edema. In our study, similar visual acuity was achieved in both groups at 1 year, with comparable numbers of patients with increased BCVA (82.7% in group 1 and 71.6% in group 2). Visual acuity was lower initially in the first group due to cataract; therefore, they achieved significantly greater visual gains compared to group 2 as a result of cataract surgery. At 1 year, the patients who underwent cataract surgery had received 0.5 more injections on average compared to patients without cataract, but the difference in injection numbers was

not statistically significant. This suggests that any possible reactivation of neovascular vessels due to cataract surgery can be controlled with ranibizumab. When anatomic responses were evaluated, the rate of subretinal exudation was similar between the two groups. However, the patients who underwent cataract surgery showed higher rates of intraretinal cyst and smaller decrease in retinal thickness, although the differences were not statistically significant. Based on the aforementioned studies and our study, anti-VEGF therapy after cataract surgery halts and reverses active exudation and increases visual acuity in patients with neovascular AMD.

Cataract surgery was reported to cause an increase in choroidal thickness.[20] The drop in intraocular pressure and rise in ocular perfusion pressure accompanied by increased choroidal thickness may be associated with increased inflammation due to elevated prostaglandin and cytokines, which are thought to cause cystoid macular edema in the retina.[19,20,21,22] However, in our study, there was no significant difference in choroidal thickness between the patients who did and did not have cataract surgery, and choroidal thickness decreased in both groups due to anti-VEGF use.

Conclusion

In conclusion, cataract surgery provides significant visual improvement in patients with active AMD. No unfavorable impact on AMD progression was observed in eyes that underwent cataract surgery while receiving anti-VEGF therapy. Combined cataract surgery and anti-VEGF therapy can be considered an effective and reliable treatment modality in patients with active neovascular AMD.

Ethics

Ethics Committee Approval: Ethics Commettee of Muğla Sıtkı Koçman University Faculty of Medicine-18.04.2018-05/III.

Informed Consent: Obtained.

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Authorship Contributions

Surgical and Medical Practices: Sabahattin Sül, Aylin Karalezli, Müjdat Karabulut, Concept: Sabahattin Sül, Aylin Karalezli, Müjdat Karabulut, Design: Sabahattin Sül, Aylin Karalezli, Müjdat Karabulut, Data Collection or Processing: Sabahattin Sül, Aylin Karalezli, Müjdat Karabulut, Analysis or Interpretation: Sabahattin Sül, Aylin Karalezli, Müjdat Karabulut, Literature Search: Sabahattin Sül, Aylin Karalezli, Müjdat Karabulut, Writing: Sabahattin Sül, Aylin Karalezli, Müjdat Karabulut.

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Original Article

The Effect of Smoking on Macular, Choroidal, and Retina Nerve Fiber Layer Thickness

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Abstract

Objectives: This study aimed to compare the thickness of the macula, choroid, and peripapillary retina nerve fiber layer (RNFL) in smokers with those of healthy, nonsmoking individuals using spectral domain optical coherence tomography (SD-OCT).

Materials and Methods: Sixty-eight healthy smokers with an average of 19.75 pack-years and 71 nonsmoker subjects (control group) were included in the study. Macular thickness, RNFL thickness, and choroidal thickness (CT) were measured by SD-OCT.

Results: The mean age of the smokers was 42.76±6.97 years and that of the control group was 41.15±11.61 years (p=0.32). Inferonasal and temporal RNFL thicknesses were 121.60±27.40 µm and 69.75±9.82 µm in the smokers group and 109.05±21.71 µm and 75.95±15.01 µm in the nonsmoker group, respectively. The differences were statistically significant (p=0.003, p=0.005, respectively). Central macular thickness (CMT) was 222.97±18.95 µm and subfoveal CT was 369.52±105.36 µm in the smoker group, while these values were 222.98±17.72 µm and 347.42±104.63 µm in the nonsmoker group, respectively. There were no significant differences in these comparisons (p=0.99, p=0.49, respectively). A significant negative correlation was found between smoking exposure and nasal and temporal CT.

Conclusion: The results of our study revealed that RNFL thickness was decreased but CMT and CT were not affected in healthy chronic smokers.

Keywords: Smoking, retinal thickness, choroidal thickness, spectral domain optical coherence tomography

Introduction

Nicotine addiction is one of the most significant and preventable health problems of our time. The World Health Organization predicts that by the year 2030, 9 million people worldwide will die annually due to cigarette smoking.[1,2] Over 4,000 chemicals in cigarette smoke are known to affect the pulmonary and cardiovascular systems, and smoking is a well-known risk factor for atherosclerotic and thromboembolic events.[3] Smoking is also a risk factor for the development of several ocular pathologies such as age-related macular degeneration, ischemic optic neuropathy, hypertensive retinopathy, cataract, glaucoma, thyroid orbitopathy, keratoconjunctivitis sicca, and strabismus in the offspring of smoking parents.[4,5,6] Quantitative analysis of choroidal vasculature is necessary to understand the pathophysiology of choroidal disorders and to evaluate chorioretinal diseases. However, the mechanisms underlying the relationship between ocular vascular diseases and smoking are not yet known.[7] One such method of analysis is the measurement of choroidal thickness (CT). CT has been shown to be affected by choroidal blood flow.[8] Spectral-domain optical coherence tomography (SD-OCT) with special software programs (e.g., enhanced depth imaging) is an established method of measuring CT.

With these developments, researchers have the opportunity to examine the effect of cigarettes on the retinal and choroidal layers in more detail. The aim of the current study was to evaluate the effects of smoking on macular, choroidal, and retina nerve fiber layer (RNFL) thickness using SD-OCT.

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Materials and Methods

This cross-sectional study was performed in the Department of Ophthalmology of the Düzce University Faculty of Medicine (Düzce, Turkey) between December 2016 and June 2017. Approval for the study was obtained from the university ethics committee and written informed consent forms were signed by all the participants in compliance with the requirements of the Declaration of Helsinki. The study group consisted of healthy cigarette-smoking individuals who had no systemic or ocular disease (smoker group). Age- and gender-matched healthy individuals who had never smoked cigarettes formed the control group (nonsmoker group). In all participants, only the right eye was evaluated.

The criteria for inclusion in the study included spherical refraction between +1.0 and -1.0 diopters, best-corrected visual acuity of 20/20 or better, and axial length (AL) <25 mm. No evident systemic disease was detected in any of the study participants upon general physical examination and biochemical laboratory analyses. Subjects whose history or examinations revealed Alzheimer's or neurological diseases such as multiple sclerosis were excluded. Upon ophthalmologic examination, no pathological findings (e.g., cornea opacities, cataract, glaucoma, media opacities, optic neuropathy) were detected in any of the subjects. Subjects who had high refractive errors, were under local or systemic medication, had used/been exposed to any neurotoxins or drugs, or had a history of ocular or systemic diseases were excluded from the study. In order to eliminate the potential influence of alcoholism or malnourishment, only those heavy smokers with good dietary habits who were healthy and did not use alcohol were selected for the study. All participants were prohibited from smoking for at least 8 h prior to taking measurements to avoid the acute effects of cigarette chemicals on the eye. In addition, the subjects were instructed not to consume any alcohol or caffeine for at least 12 h before measurements were taken.

Ophthalmological Examinations

Demographic data were collected from all study participants. After performing refraction measurements, all subjects were tested for best-corrected visual acuity using the Snellen chart. Intraocular pressure was measured via Goldmann applanation tonometry (Nikon, Tokyo, Japan), followed by slit-lamp examination. Three drops of tropicamide and 2.5% phenylephrine were topically instilled at 5-min intervals and after a period of approximately 30 min, the subjects underwent binocular indirect ophthalmoscopy. Clinic ophthalmologists performed the dilated fundus examinations. AL measurements were then conducted with the Echoscan US 500 (Nidek Co. Ltd., Aichi, Japan). The same ophthalmologist carried out all the OCT scans to ensure consistency of results. These scans were conducted immediately after pupil dilation and again on the morning after the examination (between 8:00 and 9:00 am).

The Heidelberg Spectralis (version 1.5.12.0; Heidelberg Engineering, Heidelberg, Germany) was employed to measure the macula and peripapillary RNFL (G: global, T: temporal, Ts: temporal superior, Ti: temporal inferior, N: nasal, Ns: nasal superior, Ni: nasal inferior). All SD-OCT images were obtained between 9:00 and 12:00 am. The Heidelberg Spectralis performed conventional OCT scans as well as enhanced depth imaging OCT, in which an inverted image of the choroid was obtained with the device positioned close to the eye. A 5°-30° rectangle incorporating the macula and optic nerve was divided into sections. Eye tracking was used to generate 100 average scans per section.

Central foveal thickness and CT were measured from the horizontal section running straight through the center of the fovea using the Heidelberg Spectralis.[9] Central foveal thickness was measured as the distance between the inner border of the hyperreflective line representing the internal limiting membrane and the inner border of the hyperreflective line representing the retinal pigment epithelium; CT was measured from the outer border of the hyperreflective line ascribed to the retinal pigment epithelium to the hyperreflective line of the inner sclera border. Seven measurements (one subfoveal, three temporal, and three nasal) were taken at 500 µm intervals up to 1500 µm via the software caliper. All participants completed the study.

Statistical Analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software (v17.0 for Windows; SPSS Inc., Chicago, IL, USA). Descriptive statistics were determined as means ± standard deviations. Student's t-test was used to compare qualitative data with normal distribution, and the Mann-Whitney U-test was used to compare parameters without normal distribution. Pearson correlation analysis was used to investigate associations between the parameters. P values <0.05 were considered statistically significant.

Results

Evaluations were carried out on 68 eyes of 68 smokers (46 male, 22 female) and 71 eyes of 71 nonsmokers (46 male, 25 female). Median smoking exposure was 20 pack-years (range: 1-121). Table 1 shows the demographic and clinical characteristics of these groups and their statistical significance.

There were no significant differences in age or gender between the smoker and nonsmoker groups. Mean intraocular

Table 1. Demographic characteristics of the study participants

	Smokers (n=68)	Controls (n=71)	p
Age, years (mean ± SD)	42.76±6.97	41.15±11.61	0.32
Males (n)	46	46	1.00
Females (n)	22	25	0.66
Pack-years*	19.75±11.62	0	0.01
IOP (mmHg)	17.65±3.43	18.40±2.92	0.40
AL (mm)	22.95±0.82	22.93±1.01	0.92

*Pack-year: number of packs smoked per day × number of years smoking.
IOP: Intraocular pressure, AL: Axial length, SD: Standard deviation

pressure was 17.65±3.43 mmHg in the smoker group and 18.40±2.92 mmHg in the control group (p=0.40).

The mean AL in the smoker and nonsmoker groups was 22.95±0.82 mm and 22.93±1.01 mm, respectively (p=0.92). In the smoker group, RNFL thickness was 121.60±27.40 µm in the inferonasal quadrant and 69.75±9.82 µm in the temporal quadrant; these values were 109.05±21.71 µm and 75.95±15.01 µm respectively in the nonsmoker group. Intergroup differences in these two values were statistically significant (p=0.003 and p=0.005, respectively). There were no significant differences between the groups in peripapillary RNFL thickness in the other quadrants (Table 2).

Central macular thickness (CMT) and subfoveal CT were 222.97±18.95 µm and 369.52±105.36 µm in the smoker group, compared to 222.98±17.72 µm and 347.42±104.63 µm in the nonsmoker group, respectively. Neither parameter was significantly different between the groups (p=0.99 and p=0.49, respectively).

The groups did not show any significant difference in nasal and temporal CT at 500, 1000, and 1500 microns (p>0.05) (Table 3). Table 4 shows a significant negative correlation between CT and smoking exposure; however, the degree of association was weak.

Discussion

The aim of the present study was to assess the influences of smoking on the macula, RNFL thickness, and CT. The study found that the smoker and nonsmoker groups were not significantly different in terms of CMT and CT measurements. Except for the temporal and inferonasal quadrants, there were no statistically significant differences between the two groups in terms of RNFL thickness.

The exact mechanisms of the effects of smoking on blood vessels have not been fully clarified and are still being investigated in several models. The vasoactive compounds found in cigarettes increase choroidal vascular resistance by causing vasospasm in the circulatory system. The resulting constriction of the posterior ciliary arteries can cause anterior ischemic neuropathy.[10,11] Nicotine and carbon monoxide have been shown to accelerate atherosclerosis, and if the ophthalmic branch of the internal carotid artery is involved, ocular ischemic episodes such as amaurosis fugax could result.[12] Studies have also shown cigarette smokers to have higher levels of erythrocytes, leukocytes, and plasma fibrinogen.[12,13,14] Elevated levels of these blood and plasma components may increase the risk of thrombosis caused by hyperviscosity. Nicotine prompts vasoconstriction by stimulating alpha-adrenergic receptors, while the carbon monoxide found in cigarettes binds to hemoglobin, thus decreasing its oxygen transport capacity.[15] Some studies focused on endothelial dysfunction and oxidative stress. Studies of endothelial dysfunction have reported evidence that the body's production of endothelium-derived substances (e.g., nitric oxide, endothelin, angiotensin-converting enzyme, and tissue plasminogen activator) is altered after the ingestion of cigarette smoke.[16] Free radicals that are either inhaled by the smoker or endogenously produced via xanthinoxidase, NADPH oxidase, or peroxidase enzymes initiate oxidative stress mechanisms. Oxidative stress products lead to abnormal nitric oxide activity, vasomotor dysfunction, smooth muscle proliferation, inflammatory cells, and thrombocyte activation.[17]

Table 2. The mean peripapillary retina nerve fiber layer thickness measured by spectral domain optical coherence tomography for smokers and controls

Peripapillary retinal quadrants	Smokers (n=68)	Controls (n=71)	p
Temporal (µm)	69.75±9.82	75.95±15.01	0.005
Superotemporal (µm)	140.38±33.90	142.12±20.06	0.71
Inferotemporal (µm)	143.80±20.32	145.70±22.43	0.60
Nasal (µm)	80.72±15.19	79.05±14.96	0.51
Superonasal (µm)	118.54±25.20	112.45±16.55	0.09
Inferonasal (µm)	121.60±27.40	109.05±21.71	0.003
Global (µm)	101.63±13.26	102.43±9.42	0.68

Table 3. Evaluation of central macular thickness and subfoveal, nasal, and temporal choroidal thickness in the groups

	Smokers (n=68)	Controls (n=71)	p
CMT (µm)	222.97±18.95	222.98±17.72	0.99
Subfoveal CT (µm)	369.52±105.36	347.42±104.63	0.49
Nasal 500 µm CT (µm)	357.95±97.41	340.18±106.04	0.30
Nasal 1000 µm CT (µm)	350.57±98.49	330.23±100.65	0.23
Nasal 1500 µm CT (µm)	330.01±98.46	312.92±103.10	0.32
Temporal 500 µm CT (µm)	353.42±103.61	346.05±99.28	0.66
Temporal 1000 µm CT (µm)	338.57±100.0	335.02±96.36	0.83
Temporal 1500 µm CT (µm)	325.11±102.04	324.85±97.37	0.98

CMT: Central macular thickness, CT: Choroidal thickness

Table 4. Relationship between smoking exposure and choroidal thickness

Choroidal thickness	Smoking exposure (pack-years)	
	r	p
Subfoveal	-0.217	0.075
Nasal 500 µm	-0.255	0.036
Nasal 1000 µm	-0.326	0.007
Nasal 1500 µm	-0.375	0.002
Temporal 500 µm	-0.352	0.003
Temporal 1000 µm	-0.283	0.019
Temporal 1500 µm	-0.334	0.005

These effects on the circulatory system lead to ischemia and hypoxia in the tissue of cigarette smokers.

A few studies have evaluated the thickness of some retinal layers in smokers using OCT.[18,19,20,21] Kumar et al.[18] showed evidence that RNFL thinning increased more in smokers than in nonsmokers; however, the RNFL thickness in moderate smokers and severe smokers was not significantly different except in the nasal quadrant. Dervisoğulları et al.[19] showed that mean RNFL was significantly thinner in the smoker group compared to a control group. They also reported that the inferior, superior, nasal, and temporal RNFL thicknesses were 123.1±26.1, 117.0±5.5, 64.9±8.6, and 63.5±6.8 μm in the smoker group and 130.8±11.8, 123.5±11.0, 72.4±9.8, and 58.4±7.4 μm in the nonsmoker group. Inferior and superior RNFL were significantly thinner in the smoker group (p=0.01 and p=0.03, respectively), while the nasal and temporal quadrants did not differ significantly (p=0.07 and p=0.96, respectively). In addition, the ganglion cell-inner plexiform layer complex was not significantly altered by chronic smoking.[19] RNFL thinning has also been reported in chronic heavy cigarette smokers, and the explanations regarding the root of tobacco optic neuropathy (TON) should be explored in general to understand the underlying mechanisms.[20] The association between smoking and TON development is attributed to the generation of reactive oxygen species and decreased blood flow due to the vasoconstrictive effect of nicotine.[21] Additionally, cigarettes include cyanogen, a precursor of cyanide neurotoxin, which appears to contribute to TON.[22]

Duman et al.[23] found that the RNFL thickness and all the layers of retina in healthy smokers and controls did not differ significantly. Demirci et al.[24] reported that migraine patients who smoked exhibited decreased RNFL thickness when compared to both nonsmoking migraine patients and healthy controls. The mean and nasal RNFL thicknesses in the nonsmoker migraine patients were significantly lower than in the control group and the mean, nasal, and inferior RNFL thicknesses in the smoking migraine patients were significantly lower than in the control group. Moreover, the patients with and without aura did not show a significant difference in RNFL thicknesses. Smoking reduces retinal blood flow and hyperoxia autoregulation ability of retinal vessels due to the vasoconstrictive influences of nicotine and changed endothelial function.[25,26]

Pathological factors (polypoidal choroidal vasculopathy and central serous chorioretinopathy), pharmaceutical factors (intravitreal ranibizumab), age, axial length, refractive status, diurnal rhythm, and perfusion pressure are all recognized as causal factors in CT variation, although most of those affecting subfoveal CT have still not been identified.[27,28,29,30,31,32] In the present study, there were no significant age, gender, or AL differences between the study and control groups. Previous studies have shown that the choroid is thicker in males than females.[7] Although 67% of the smokers were male, no significant differences in CT were found between the two groups. The present study was conducted in the morning, as CT is known to progressively decrease after wakening from sleep.[32] Dervişoğulları et al.[19] demonstrated that chronic smoking does not significantly affect CT. In their study, the subfoveal CT was detected to be 304.0 in the smokers and 308.2 μm in the non-smokers. Sizmaz et al.[8] reported smoking just one cigarette led to a significant decrease in CT lasting for at least 3 h although the initial CT measurements of the smokers and nonsmokers were not significantly different. The CT in the non-smokers was unchanged.

Our data support those findings. We observed smokers and nonsmokers to have similar CT except during the acute phase. In our study, smokers were prohibited from smoking during the 8-h period before their SD-OCT test and thus, this intense reaction was not observed.

Kantarcı et al.[4] reported that macular and choroidal thicknesses in long-term smokers were observed to be similar to those of healthy non-smokers. Ulas et al.[33] did not observe any significant difference in retinal or choroidal thicknesses between smokers and nonsmokers. However, they noted that choroid was thicker in smokers the first 5 minutes after cigarette consumption but returned to baseline levels after 1 hour. They argued that the difference in results between the two studies could be due to different alignment and recording algorithms for OCT screening and different methods used for screening.[33]

Wimpissinger et al.[34] reported that smokers showed significantly higher choroidal blood flow at baseline than nonsmokers on laser Doppler flowmetry. The increase in blood flow in nonsmokers due to carbogen respiration was found in comparison to the relatively stable blood flow in smokers. Besides, carbogen respiration did not make a significant difference in systemic hemodynamics, optic nerve head blood flow, retinal vessel diameters and blood gas values between groups. Though there were not many studies in this respect, the writers suggested an abnormal choroidal vascular responsiveness in the smokers.

Garhöfer et al.[35] indicated that habitual smokers demonstrate impaired retinal vascular function. In their study, long-term smokers showed significantly reduced flicker-induced vasodilatation in major retinal veins, leading to a decreased response in retinal blood flow.[5] Kool et al.[36] determined that smoking caused acute hemodynamic and vascular fluctuations, but that there was no difference between the hemodynamic and vascular properties of the chronic smokers and nonsmokers. This finding concurs with that of the present study, which found CT in smokers and nonsmokers to be similar.

Correlation analysis in our study revealed a significant negative correlation between smoking exposure and CT. Sigler et al.[37] also observed a negative correlation between them.

Study Limitations

One limitation of the current study was the small sample size. Moreover, body mass index, systemic blood pressure, and plasma lipid level measurements were not included and this shortcoming might have affected CT. In addition, cessation of smoking 8 h before the measurement of CT might alter our results. We speculate that the choroidal vessels showed a reflexive dilation, resulting in the choroid being thicker than normal.

Hence, in future studies, all of the smokers should be measured again without altering their normal smoking habits.

Conclusion

In conclusion, the findings of the present study suggest that RNFL thickness is decreased in healthy heavy cigarette smokers, while CMT and CT are not affected. RNFL differences may be associated with endothelial dysfunction and retinal vascular reactivity caused by smoking. Further studies employing larger sample numbers are needed to identify the possible acute and chronic impacts of smoking on the thickness of the retina and choroid.

Ethics

Ethics Committee Approval: Düzce University Faculty of Medicine Ethics Committee decision no: 2017/75.

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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Original Article

Approach of Family Physicians to Pediatric Eye Screening in Diyarbakır

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Abstract

Objectives: In Turkey, preventive medicine services are the responsibility of family physicians and vision screening is a key component of this responsibility. In this study, we aimed to investigate the approach of family physicians to vision screening in infants and children.

Materials and Methods: Data were collected using a 16-item questionnaire administered to 100 family physicians working in the center and provinces of Diyarbakır.

Results: The results indicated that 88 (88%) physicians declared knowing what the red reflex test was, while 12 physicians declared that they had never heard of it. Only 16 (16%) physicians performed the test routinely and 36 (36%) physicians performed it only in suspicious cases. Ten (10%) physicians indicated that they did not refer the patients to an ophthalmologist even though they did not perform the red reflex test. Moreover, 5 (5%) physicians did not have an ophthalmoscope and 12 (12%) physicians reported not knowing how to use an ophthalmoscope. Forty (40%) of the physicians measured preschool visual acuity at least once. Sixty-six (66%) physicians referred younger children who could not express their vision problems to an ophthalmologist. Four (4%) physicians declared that they would delay surgery in children with strabismus until they were old enough for surgery. Ninety-three (93%) physicians suggested that educational seminars about vision screening would be beneficial.

Conclusion: Educational seminars about vision screening may have favorable outcomes. The medical devices in family medicine centers should be improved. Vision screening can be added to the negative performance-based compensation system in order to increase physicians' attention to vision screening. To implement detailed eye screening programs like those in developed countries, an infrastructure should be established for this screening program.

Keywords: Red reflex test, eye screening, congenital cataract, retinoblastoma, negative performance

Introduction

The practice of family medicine in Turkey was first initiated in Düzce in 2005, and its nationwide expansion began as of 2010. The duties and responsibilities of family physicians are defined as approaching registered individuals holistically and providing individualized preventive, therapeutic, and rehabilitative health services as part of a team. Preventive medical services personally provided by family physicians include vaccination, pregnancy follow-up, and infant/child care.[1]

Examination of the eye and adnexa is an important component of infant/child care. Red reflex examination is a simple, non-invasive screening test that can easily be performed by family physicians. The red reflex occurs when light from the ophthalmoscope passes through the transparent structures of the eye and is reflected by the fundus back to the eye of the examiner.[2] This test enables early diagnosis of important and treatable sight- and life-threatening diseases such as congenital cataracts and retinoblastoma.[3] In their statement issued in 2016, the American Academy of Pediatrics recommended performing

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red reflex examination at every physician visit for babies aged 0-6 months, and again at 6 months, 12 months, 1-3 years, 4-5 years, and 6 years old.[4]

In childhood, eye problems such as refractive errors, amblyopia, and strabismus may result in functional and preventable visual impairment or even blindness. Vision screening conducted at schools in Southeastern Anatolia in 2013 revealed that 10.6% of the children had refractive errors that required correction and were unrecognized by the children themselves. In the same study, amblyopia was detected in 2.6% of children, and the most frequent causes of ambylopia were reported as anisometropia and strabismus.[5] These preventable causes of visual impairment are issues that should be addressed by the family physicians in pediatric ophthalmology follow-up visits as part of preventive medicine.

The Southeastern Anatolia region includes the lowest ranked cities in Turkey in terms of socio-economic development.[6] It is especially important for family physicians to exercise due diligence in the practice of preventive medicine in this region. In this study, we conducted a survey of family physicians working in the province of Diyarbakır. Our aim was to analyze the approach of physicians in this region to eye screening tests for infants and children, evaluate how knowledgeable and equipped they are, and to determine whether they require continuing education on this topic.

Materials and Methods

The study protocol was approved by Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee, and the study was carried out in accordance with the principles of the Declaration of Helsinki. A questionnaire consisting of 16 items pertaining to eye screening tests for infants and children was created (Table 1). Questions were prepared based on internationally recommended pediatric eye screening tests. The aim was to determine to what degree these screening tests are known and performed by family physicians, evaluate their level of knowledge and awareness of the subject and the availability of necessary equipment, and learn their views on the need for further education on this topic. Of 492 family physicians working in the urban center and surrounding districts of the Diyarbakır province, 100 were contacted. The questionnaire was administered to the family physicians participating in the study. Data were recorded and the results were calculated as percentages.

Results

One hundred family physicians working in the central and surrounding districts of the Diyarbakır province participated in this survey. When asked what the red reflex test is, 88 (88%) of the physicians said they knew of this test, while 12 (12%) stated they had never heard of it. When the 88 physicians who knew about the red reflex test were asked whether they perform it, 52 (52%) stated that they did red reflex examination, while 36 (36%) stated they had never performed it despite knowing of it. Only 16 (16%) of 52 physicians who performed the red reflex test stated that they did so regularly, while 36 (36%) reported that they performed it only in suspicious cases. Of these 52 physicians, 1 reported detecting an absent red reflex only once, and another reported detecting absent red reflex 3 times. Among all the physicians participating in the survey, the proportion who regularly performed red reflex examination was found to be 16%. Of the 36 physicians who never did red reflex screening, 10 (10%) stated that they did not refer infants to an ophthalmologist despite not performing the test. Thirty-three (33%) of the participating physicians were aware that the red reflex test should be performed in every infant examination. Seventy-two physicians (72%) stated that it would be beneficial to add the red reflex test to follow-up charts, just like height and weight measurements

The physicians were asked before what age (in months) congenital cataracts should be treated to avoid the development of amblyopia. Only 31 physicians (31%) responded correctly, while 69 physicians (69%) did not know about the timing of treatment even though they detect congenital cataracts. When asked whether their practices were equipped with a direct ophthalmoscope, 95 physicians (95%) indicated that they had an ophthalmoscope, while 5 physicians (5%) did not. Thirty-five (35%) of the physicians reported never using a direct ophthalmoscope, 12 (12%) of whom stated that they did not know how to use an ophthalmoscope.

Table 1. Survey questions

Routine eye screening in infants and children
Are you working as a specialist family physician or a general practitioner family physician?
How many years have you been working as a family physician?
Do you know what red reflex examination is?
Do you perform red reflex screening?
How frequently do you perform red reflex screening?
How many times have you detected absent red reflex to date?
If you do not performing this screening, do you refer the infant to an ophthalmologist?
Do you know that red reflex screening should be performed in every infant examination?
Before what age (months) should congenital cataract be treated in order to avoid amblyopia?
Is there a direct ophthalmoscope in your practice?
Do you ever use the direct ophthalmoscope?
If you do not use your direct ophthalmoscope, why not?
Do you measure children's visual acuity in both eyes, one eye at a time, using a preschool chart?
If you do not assess visual acuity, do you refer the child to an ophthalmologist?
What do you do when you detect strabismus in an infant or child?
Do you think an educational seminar on these topics should be held for family physicians? Would you like to attend such a seminar?

The physicians were asked questions about eye screening tests for pediatric patients. Forty (40%) of the physicians reported measuring children's visual acuity in both eyes separately using a preschool chart. Sixty-six (66%) of the physicians referred children who were too young (1-4 years old) to describe their visual acuity using a chart to an ophthalmologist for refraction examination. When asked about their approach to strabismus in infants or children, 96 physicians (96%) stated that they would refer the patient directly to an ophthalmologist, and 4 physicians (4%) said they would take no action until the patient was old enough to undergo surgery.

When asked whether an educational seminar should be held for family physicians regarding eye screening tests for infants and children, 93 (93%) of the physicians answered positively and stated that they would like to attend if such a seminar was held.

Approximately half of the physicians did not want to share for how long they had been working as family physicians and whether they were general practitioners or specialists. As a result, the survey responses could not be compared based on these data.

Discussion

Red reflex examination was first described by Bruckner in 1962 and was recognized as a method to screen for vision- and life-threatening eye diseases in children.[3] The ophthalmoscope works on the principle that light entering the patient's pupil passes through the transparent ocular structures and is reflected from the fundus back to the observer. When the cornea, aqueous humor, crystalline lens, and vitreous are transparent, the reflection will be red, yellow, orange, or a combination of these colors.[2] In conditions that obstruct the passage of light (e.g., cataract) or prevent the proper reflection from the ocular fundus (e.g., retinoblastoma), the reflection will appear black, white, or nonhomogeneous.[3,7]

In 2016, the American Academy of Pediatrics recommended performing red reflex examination at every physician visit for babies aged 0-6 months, and again at 6 months, 12 months, between 1-3 years, 4-5 years, and at 6 years old.[4] Red reflex screening protocols are followed in many developed countries. For instance, red reflex screening is performed in more than 90% of pediatric and neonatal units in Sweden and was reported to have tripled the detection rate of ocular pathologies (from 19% to 64%).[8]

In order to prevent visual impairment caused by congenital cataracts in newborns, surgery must be done within 6 weeks of birth.[9] Detecting congenital cataracts this early is only possible if pediatricians or family physicians perform red reflex examination. In a study conducted in the United Kingdom, it was found that less than half of congenital cataracts detected between 1995-1996 were detected by screening before the age of 8 weeks.[10] A study in the United States of America reported that 38% of congenital cataracts were detected after 6 weeks.[11] Another disease that can be detected by red reflex examination is retinoblastoma. Retinoblastoma, the most common primary intraocular tumor in childhood, leads to leukocoria. A study on retinoblastoma determined that only 123 (8%) of 1831 children with leukocoria were detected by a pediatrician.[12]

There are no data in Turkey regarding what proportion of congenital cataract and retinoblastoma are detected by family physicians using red reflex examination. In the present study, family physicians were questioned about their knowledge and practice of red reflex screening. Twelve percent of the respondents stated that they had never heard of the red reflex test, while 36% stated that they knew of but had never performed it. Only 16% of the physicians performed red reflex screening regularly. Thirty-three (33%) physicians expressed that they knew this screening should be performed in every infant examination. Twelve physicians (12%) did not know how to use a direct ophthalmoscope. Even if able to detect congenital cataract, only 31% of the respondents were aware that the baby must undergo cataract surgery before the age of 6 weeks. Awareness of this issue must be raised among family physicians in Turkey to facilitate the timely detection of vision- and life-threatening diseases such as congenital cataracts and retinoblastoma.

Eye screening during childhood is important to prevent amblyopia secondary to refractive error and strabismus. Legislative decree no: 633 issued in 2011 stated that the family physician is responsible for the overall health of school-age children and must provide diagnostic and therapeutic services for the health problems of school-age children.[13] However, an eye screening program carried out in schools in Southeastern Anatolia in 2013, refractive errors that required glasses and were unnoticed by the child were detected in 10.6% of children, and amblyopia was detected in 2.6% of children. The two most frequent causes of amblyopia were found to be anisometropia and strabismus.[5] In a study performed in Turkey in 2017, approximately 823 primary school children living in İstanbul underwent eye screening and it was reported that 22% of children in private schools and 65% of children in public schools had never had a vision test before. The authors also emphasized that previously unrecognized vision problems were twice as common in children from a lower socio-economic background.[14] These two studies suggest that, despite the decree, the diagnostic and therapeutic services provided to school-age children by family physicians are inadequate in terms of eye health. In our study, 40 physicians (40%) measured the visual acuity of preschool children in both eyes separately using an appropriate chart. For the younger age groups, 66% of the physicians referred children to an ophthalmologist for refraction test. These results show that almost half of the children in the Diyarbakır province begin school without ever undergoing a refraction test.

Strabismus can develop in the absence of an underlying cause or due to severe pathologies like retinoblastoma.[15] When we asked the family physicians about their approach to children in whom they detected strabismus, 4 physicians (4%) stated that they would wait until the patient was old enough to undergo

surgery. However, there is no specified age for strabismus surgery; therefore, making the patient wait can result in delayed treatment of potentially vision- and life-threatening pathologies. It is important to make physicians aware of this.

Infant and child eye examinations are included in routine screening tests in developed countries. For example, visual acuity assessment has been a part of the screening program in the Netherlands since 1960. Every 5 years, the nurses and physicians responsible for the screening participate in a one-day training program led by a screening director and orthoptist. Patients have a total of 7 free eye screenings (at 1, 2, 3, 6-9, 14-24, 36, and 45 months of age). Examinations done between 1 and 4 months of age include inspection of the eye and adnexa, red reflex examination, Hirschberg test, and pupillary light reflex test. Examinations done between 6 and 24 months of age include inspection of the eye and adnexa, Hirschberg test, pupillary light reflex test, cover-uncover test, alternate cover test, and assessment of eye movement and monocular tracking. Visual acuity is measured using the Amsterdam Picture Chart at 36 months and the Landolt C graph at 45 months of age.[16] While such detailed eye screening tests are standard in developed countries, there is still a conspicuous lack of regular screening programs in our country.

In article 24 of the regulations governing the practice of family medicine issued in an Official Gazette in 2013, an ophthalmoscope and Snellen chart are included in the minimum necessary medical device and equipment list for family health centers.[17] Of the physicians who participated in our survey, 5 (5%) stated that they did not have ophthalmoscope in their center. This indicates that family health centers are not being adequately inspected in terms of medical devices and equipment.

The concept of negative performance-based compensation in family medicine is defined in the Family Medicine Law no: 5258 issued in 2004, article 3, section 7 entitled "Personnel status and financial rights" as follows: In the event of incomplete provision of preventive medical services according to the standards determined by the Ministry of Health, up to 20% of the gross charge shall be deducted from payment".[1] Clause d of article 4 of this law specifies vaccination, pregnancy follow-up, and infant-child follow-up as preventive medical services that must be provided. Deficiencies in preventive medicine practices apart from these services are not included in the implementation of negative performance-based pay. We believe that pediatric eye screening must be included in the scope of negative performance in order to improve adherence to these guidelines.

Conclusion

In conclusion, family physicians in Turkey must be better informed about which eye tests should be done for infants and children and at what ages they must be performed. Educational seminars can be held on this topic. Including infant and child eye screening tests in the negative performance-based compensation scheme will increase awareness of this subject. It is also important to begin establishing the infrastructure necessary to perform detailed ophthalmologic screening programs in our country.

Ethics

Ethics Committee Approval: The study protocol was approved by Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee, and the study was carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Review

Current Therapeutic Approaches to Chronic Central Serous Chorioretinopathy

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Abstract

Central serous chorioretinopathy (CSCR) is the second most common maculopathy after diabetic maculopathy between the third and fifth decades of life. CSCR is characterized by serous neurosensory retinal detachment occasionally coexisting with retinal pigment epithelium (RPE) detachment. CSCR usually has good clinical prognosis, often resolving spontaneously within the first three months. However, some patients may have recurrent episodes and chronic disease. CSCR can cause permanent visual loss due to persistent neurosensory retinal detachment and RPE atrophy, especially in chronic cases. In recent years, verteporfin-photodynamic therapy applied with standard and low-dose/low-fluence protocols, anti-vascular endothelial growth factors, glucocorticoid antagonists, mineralocorticoid receptor antagonists, and subthreshold micropulse laser with varying parameters have been investigated as treatment options. In this review, we evaluated randomized and non-randomized case series conducted after 2000 that included at least 3 patients with chronic CSCR over 3 months in duration who were treated with current treatment options for chronic CSCR.

Keywords: Central serous chorioretinopathy, subthreshold micropulse laser, anti-vascular endothelial growth factor, verteporfin photodynamic therapy

Introduction

Central serous chorioretinopathy (CSCR) is characterized by serous neurosensory retinal detachment (NSD) accompanied by retinal pigment epithelium (RPE) detachment in some cases, and is the second most common maculopathy after diabetic maculopathy between the third and fifth decades of life.[1,2,3] Clinically, CSCR has a good prognosis and usually resolves spontaneously within the first 3 months.[2,3] However, approximately 5% of cases can become chronic.[1,4] Refractory NSD, which can develop in chronic CSCR, may lead to photoreceptor damage, diffuse RPE changes, RPE atrophy, and subsequent permanent vision loss.[1,2,3]

Studies on the subject have demonstrated that the two main factors involved in the pathogenesis of CSCR. The first is alterations in the autoregulatory mechanisms of choroidal circulation and the subsequent choroidal ischemia, and the second is irregularities in RPE pump function.[5,6,7] Choroidal stasis, inflammation, and ischemia due to dysregulation of regulatory proteins (glucocorticoids, mineralocorticoids, epinephrine, norepinephrine) in the choroidal circulation leads to an increase in choroidal permeability.[7,8,9,10] This hypothesis is corroborated by the presence of local and/or diffuse leakage in fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA), which are important diagnostic methods for CSCR.[5,10,11,12,13] Due to the multifactorial and complex mechanism of CSCR pathophysiology, several treatment options, such as conventional laser (CL) and verteporfin photodynamic therapy (PDT) have been tried, particularly in the treatment of the chronic type; however, CL was reported to have no significant effect on the final visual acuity or recurrence rate and to have toxic

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effect on the RPE and photoreceptors.[14,15] Although successful results were obtained with the standard protocol (full-dose, full-fluence) PDT (SP-PDT), this treatment was also observed to have toxic effects on the RPE and photoreceptors.[16,17,18] The adverse effects of CL and SP-PDT have prompted studies in recent years on the safety and efficacy of subthreshold micropulse laser (SML), verteporfin PDT with different parameters (half-dose [HD] or half-fluence [HF]), glucocorticoid antagonists, mineralocorticoid receptor (MR) antagonists, and anti-VEGF agents (Figure 1).[19,20,21,22]

This review evaluated current treatment approaches to chronic CSCR based on randomized and nonrandomized studies that accepted symptom duration of at least 3 months as chronic disease and included at least a case series (more than 3 cases).

Treatment Options

Subthreshold Micropulse Diode and Yellow Laser

Although it has long been used in the treatment of CSCR, the permanent RPE damage and scarring caused by CL led to the adoption of SML, which minimizes RPE damage with repetitive short pulses (0.1-0.2 ms) that allow the use of less energy. This feature of EML enables the laser to be applied to areas much closer to the fovea.

One drawback of applying SML with repetitive short pulses (0.1-0.2 ms) was that the laser burns were too faint to see with the eye. Ricci et al.[23] claimed that this problem could be eliminated by applying micropulse diode laser under ICGA guidance to directly visualize the affected area.

In their prospective interventional study, Chen et al.[24] observed a visual acuity increase of 3 or more letters in 15 of 26 eyes with chronic CSCR that had leakage in the juxtafoveal area and underwent SML therapy (810-nm diode laser), while 5 of the 11 eyes with widespread juxtafoveal RPE leakage required rescue PDT for subretinal fluid resorption. Similarly, Lanzetta et al.[25] observed subretinal fluid resorption at 1 month in 65% and at the end of the follow-up in 75% of 24 eyes treated with SML (810-nm diode laser) and followed for an average of 14 months. Abd Elhamid[26] achieved subretinal fluid resorption after treatment in 73% of 15 eyes with CSCR treated with SML (577-nm yellow laser). In addition, the authors specifically noted that in 9 cases, the leakage was in foveal avascular zone.

Of the comparative studies conducted to date, Scholz et al.[27] applied SML (577-nm yellow laser) to 42 eyes and HD verteporfin PDT (HD-PDT) to 58 eyes diagnosed with chronic CSCR and reported subretinal fluid resorption in 36% of the eyes subjected to SML and 21% of the eyes subjected to PDT at 6 weeks, which was not a statistically significant difference.

In contrast, Maruko et al.[28] treated 29 eyes with CSCR and typical focal leakage persisting more than 3 months, 15 with CL and 14 with SML (577-nm yellow laser), and compared their efficacy in terms of complete subretinal fluid resorption and their safety in terms of RPE damage assessed by fundus autofluorescence imaging. Their results showed no significant difference in efficacy between CL and SML (66.7% vs. 64.3%, respectively). However, RPE damage was observed in all eyes with successful outcomes after CL therapy but only in one eye treated successfully with SML. Their study highlighted that SML was at least as efficient as CL and much safer than CL in terms of RPE damage. The authors also stated that their higher success rates compared to the study by Scholz et al.[27] may be attributed to their exclusion of cases with diffuse leakage from the study. In a comparative study by Özmert et al.[29], no statistically significant difference in rates of complete resorption of subretinal fluid was observed between HF-PDT in 18 eyes and SML (577-nm yellow laser) therapy in 15 eyes with chronic CSCR (72.2% vs. 80%, respectively). In a comparative, controlled prospective study by Koss et al.[20], SML (810-nm diode laser) therapy was performed on 16 eyes and intravitreal bevacizumab treatment was performed on 10 eyes with chronic CSCR, and 26 eyes were followed as a control group. The highest rate of complete subretinal fluid resorption at 10 months post-treatment was observed in the SML group, followed by the bevacizumab group, and the differences were statistically significant (SML vs.

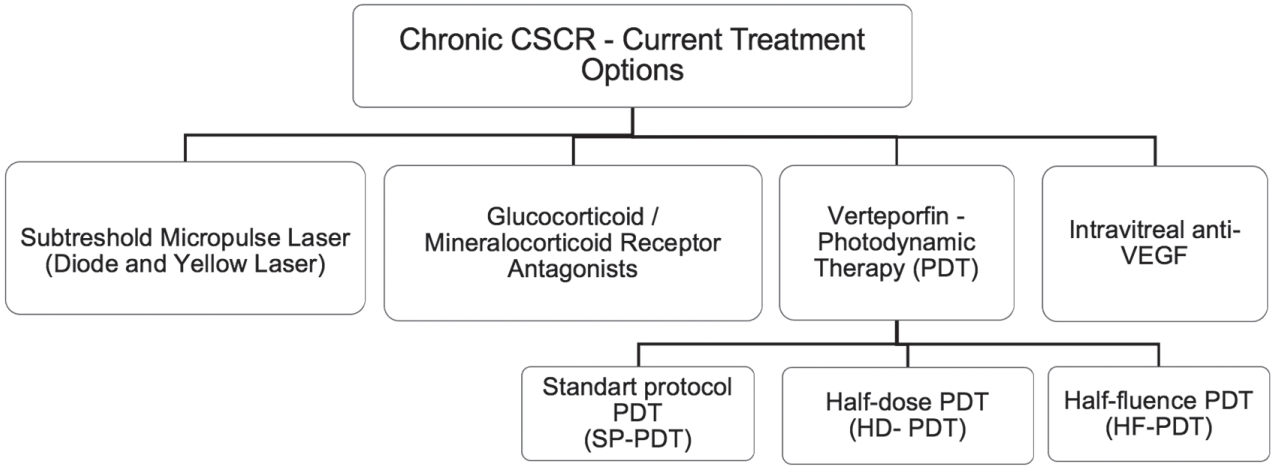

Figure 1. Current treatment options for chronic central serous chorioretinopathy

bevacizumab vs. control: 87.5% vs. 40% vs. 8%). A summary of studies on SML in chronic CSCR is presented in Table 1.

Intravitreal Anti-VEGF Therapy

Although it is known that choroidal neovascularization (CNV) is not a primary factor in the pathophysiology of CSCR,[30,31] some authors argue that anti-VEGF agents, which are the popular and effective options for treating CNV, may be effective in resolving the disease by reducing pooling and hyperpermeability in the choroidal vessels.[21,32,33] There is only one randomized controlled study on the efficacy of anti-VEGF in chronic CSCR in the literature. In this study, performed in Turkey by Artunay et al.[22], 15 eyes with a history of CSCR persisting longer than 3 months were treated with the anti-VEGF agent bevacizumab and 15 eyes were followed for 6 months without any intervention. They reported complete resorption of subretinal fluid in 80% (n=12) of the treated eyes and 53.3% (n=8) of the untreated eyes ($p<0.01$). Furthermore, visual acuity was unchanged or improved in all treated eyes and 10 eyes in the follow-up group ($p<0.01$).

In one of the nonrandomized, prospective comparative studies, Kim et al.[34] treated 30 eyes with chronic CSCR with bevacizumab. The researchers grouped eyes that did not respond to the first three injections as anti-VEGF-resistant and the eyes that responded as anti-VEGF-sensitive. Compared to the treatment-resistant group, the treatment-sensitive group showed greater subfoveal choroidal thickness and more choroidal vessel dilation in ICGA before treatment and greater reduction in choroidal thickness after treatment. Based on these findings, the authors noted the importance of the ability to predict response to anti-VEGF therapy before treatment based on subfoveal choroidal thickness and hyperpermeability. In addition to this information, Yannuzzi[35] stated that the presence of fibrin observed in the fovea on fundus examination indicates leakage from abnormal choroidal vessels and emphasized that PDT in such cases can cause severe RPE damage due to excessive energy accumulation over the fibrin structure. In light of this, anti-VEGF agents may be a better treatment option in terms of preventing potential complications in patients with subretinal fibrin accumulation. A recent meta-analysis of studies concerning anti-VEGF therapy in CSCR resulted in several recommendations.

Recommended indications for anti-VEGF in chronic CSCR[2,36,37]

1. Patients with subfoveal fibrin accumulation in which focal laser or PDT can be inconvenient
2. When CSCR is complicated by CNV

Corticosteroid Antagonists

1. Glucocorticoid Antagonists

Elevated serum cortisol levels in CSCR patients have been demonstrated previously.[9,38] Therefore, investigation began into the efficacy of anti-glucocorticoids such as ketoconazole, mifepristone, and finasteride, though only as case series.[39,40]

Some studies have also demonstrated elevated testosterone levels in CSCR.[41,42] This information prompted research into the therapeutic efficacy of finasteride, an inhibitor of 5-reductase, an enzyme that is involved in the synthesis of the hormone dihydrotestosterone (which is more potent than testosterone). In a comprehensive study on the efficacy of finasteride, Moisseiev et al.[43] administered 5 mg/day oral finasteride to 23 patients diagnosed with chronic CSCR (>3 months). After a mean follow-up time of 14.7 months, complete resolution was observed in 75.9% of the patients, while 37.5% had recurrence after discontinuing treatment. However, studies conducted with

Table 1. Major studies of subthreshold micropulse laser in the treatment of central serous chorioretinopathy

Authors	Study Designdesign	Mean duration of symptoms	Number of Eyeseyes	Follow-up Timetime	Result
Abd Elhamid[26]	Prospective, uncontrolled case series	4.6 months	15	6 months	Functional success: (mean increase in BCVA) - 27% Anatomic success: Complete response - 86.6% Recurrence rate - NA
Lanzetta et al.[25]	Prospective, uncontrolled case series	≥6 months	24	14 months	Functional success: (Mean increase in BCVA) - 30% Anatomic success: Complete or partial response - 75% Recurrence rate - NA
Chen et al.[24]	Prospective, uncontrolled case series	>4 months	26	9.5 months	Functional success: (mean increase in BCVA) - 66% Anatomic success: Complete response - 73% Recurrence rate - 31%
Özmert et al.[29]	Retrospective, comparative case series	13 months	15	12 months	Functional success: (mean increase in BCVA) - 5% Anatomic success: Complete response - 80% Recurrence rate - 13.3%

glucocorticoid antagonists were not randomized or controlled, and therefore, there is still no reliable information on the efficacy of this class of drugs.

2. Mineralocorticoid Receptor Antagonists

Several studies have demonstrated that glucocorticoids and mineralocorticoids are co-expressed in the retinal Müller cells and choroidal vessels. With higher circulating levels, these hormones bind to glucocorticoid receptors (GR) and MRs and cause alterations in retinal and choroidal homeostasis, which is considered the most likely factor in the pathophysiology of CSCR.[44,45] In a randomized controlled comparative study of MR antagonists, Pichi et al.[46] established 3 groups of 20 patients with chronic CSCR (average duration of 8 months) and administered oral spironolactone to group 1, oral eplerenone to group 2, and placebo to group 3 for the first month. For the second month, they gave eplerenone to group 1 and spironolactone to groups 2 and 3, then discontinued treatment and followed the patients for 2 more months. The authors reported that spironolactone was statistically superior in terms of visual acuity gain and subretinal fluid resolution. They attributed this difference to eplerenone having a 20-fold lower affinity for MR; however, in comparison of adverse effect profiles, they stated that eplerenone exhibits fewer progestinic effects because of its selectivity for MR. The results of other studies of MR antagonists are presented in Table 2. In summary, the MR antagonists spironolactone and eplerenone can be effective options in the treatment of CSCR. However, conducting more randomized controlled studies with these drugs will provide more reliable information regarding both treatment efficiency and adverse effect profile.

Verteporfin-Photodynamic Treatment

1. SP-PDT

The known limitations of argon laser therapy in CSCR and the roles of choroidal vessel dilation and hyperpermeability in CSCR pathophysiology have led to investigation of the efficacy and safety of verteporfin PDT, which was previously proven effective in wet AMD patients (TAP protocol),[47] in the treatment of CSCR. In the first trial evaluating the efficacy and safety of SP-PDT, carried out by Yannuzzi et al.[48] subretinal fluid resorption was observed in 60% of 20 chronic CSCR patients after a mean of 6 months. In a study by Cardillo et al.[49] in which 20 eyes with chronic CSCR were treated with SP-PDT, vision improved in 6 eyes and was unchanged in 14 eyes after an average follow-up period of 12 months, and 81% of the eyes showed complete resorption of subretinal fluid.

Ruiz-Moreno et al.[18] performed SP-PDT in 82 eyes with chronic CSCR and observed complete resorption of subretinal

Table 2. Major studies on mineralocorticoid receptor antagonist therapy (eplerenone) in central serous chorioretinopathy

Authors	Study design	Eplerenone dose	Number of eyes	Treatment duration	Outcome
Bousquet et al.[61]	Prospective, uncontrolled case series	25 mg/g (1 week), followed by 50 mg/g (1-3 months)	13	4-12 weeks	Functional success: 94% (Significant rate of increase in BCVA) Anatomic success: Complete response - 64% Partial response - 18% No response - 18%
Chin et al.[62]	Retrospective case series	50 -100 mg/g	23	4 months	Functional success: Unspecified Anatomic success: Complete/Partial response - 52.2% No response - 47.8%
Leisser et al.[63]	Retrospective case series	25 mg/g	11	10 weeks	Functional success: 73% (Significant rate of increase in BCVA) Anatomic success: Complete response - 36.4% Partial response - 27.2% No response - 36.4%
Cakir et al.[64]	Retrospective case series	25 mg/g (1 week), followed by 50 mg/g (5 weeks)	24	15 months	Functional success: 66% (Significant rate of increase in BCVA) Anatomic success: Complete response - 29% Partial response - 33% No response - 25%
Singh et al.[65]	Retrospective case series	25-50 mg/g	17	Unspecified	Functional success: Unspecified Anatomic success: Complete response - 35.3% Partial response - 11.8% No response - 47.1%

BCVA: Best corrected visual acuity

fluid in all eyes and a statistically significant increase in mean visual acuity (1.9±2.4 Snellen lines) after an average follow-up period of 12 months. In the same study, reactivation (recurring NSD) occurred in 2 eyes, CNV secondary to treatment in 2 eyes (2%), and reactive RPE hyperplasia in 9 eyes (10%). In a study including a total of 42 eyes with chronic CSCR, Reibaldi et al.[16] treated 19 with SP-PDT and 23 with HF-PDT and reported juxtafoveal CNV at 3 months in only 1 eye (2%) in the SP-PDT group. A summary of studies on SP-PDT in chronic CSCR is presented in Table 3.

2. HD-PDT and HF-PDT

Adverse effects such as focal RPE losses, CNV secondary to treatment, chronic choroidal hypoperfusion, and pigmentary changes observed after SP-PDT with verteporfin prompted clinicians to consider modifying the standard treatment protocol.

Of the clinical studies in the literature investigating the efficacy of verteporfin-PDT in CSCR, only two were done in chronic cases. Bae et al.[50] randomized 16 eyes with CSCR into two equal groups and treated one group with HF-PDT and the other with intravitreal ranibizumab injection (consecutive monthly injections); at the end of a 3-month follow-up period, they observed complete resorption of subretinal fluid in 6 eyes (75%) in the PDT group and 2 eyes (25%) in the injection group. In the same study, 4 eyes with incomplete resorption after ranibizumab injection underwent rescue HF-PDT and 2 of them showed complete resorption of subretinal fluid. No complications occurred in either group. In another randomized controlled study, Semeraro et al.[51] gave intravitreal bevacizumab (1.25 mg) injections to 12 eyes and performed HF-PDT in 10 eyes diagnosed with CSCR persisting for an average of more than 3 months, with 9 months of follow-up. At the end of the follow-up period, there were no statistically significant differences between the two groups in terms of mean central macular thickness or change in visual acuity. However, because the number of eyes with complete subretinal fluid resorption was not reported in that study, their results could not be compared in detail with those of other studies. There were also no complications secondary to treatment reported in either group in that study.

Among the studies on HD-PDT and HF-PDT, Chan et al.[19] treated 48 eyes with chronic CSCR with HD-PDT (3 mg/m^2 verteporfin) and reported complete resorption of subretinal fluid in all eyes after 12 months of follow-up and recurrence in 4 eyes (8.3%). Mean visual acuity of the patients increased by 2 lines. No complications occurred in any of the eyes in their study. In another study, Nicolo et al.[52] performed HD-PDT on 38 eyes with chronic CSCR and observed complete resorption of subretinal fluid in all eyes and recurrence in 5 eyes (13.2%) after a mean follow-up of 14.2 months, and no complications were reported. Senturk et al.[53] performed HD-PDT on 24 eyes with chronic CSCR and reported complete resorption of subretinal fluid in all of the eyes at 6 months and emphasized that no complications occurred in any of the eyes.

Table 3. Major studies on standard-protocol verteporfin-photodynamic therapy in central serous chorioretinopathy

Authors	Study design	Mean duration of symptoms	Number of eyes	Follow-up time	Outcome
Yannuzzi[35]	Prospective, uncontrolled case series	111 months	20	6.8 months	Functional success: (mean increase in BCVA) - 53% Anatomic success: Complete response - 60% Recurrence rate - 10%
Cardillo et al.[49]	Prospective, uncontrolled case series	≥6 months	16	6-12 months	Functional success: (Mean increase in BCVA) - 35% Anatomic success: Complete response - 76% Recurrence rate: 15%
Ruiz-Moreno et al.[18]	Retrospective case series	28 months	82	Success rate	Functional success: (mean increase in BCVA) - 30% Anatomic success: Complete response - 100% Recurrence rate - 2.4%
Silva et al.[66]	Retrospective case series	8.5 months	46	56.8 months	Functional success: (mean increase in BCVA) - 33% Anatomic success: Complete response - 100% Recurrence rate - 8.6%
Sakalar et al.[67]	Retrospective case series	≥6 months	17	13 months	Functional success: (mean increase in BCVA) - 84% Anatomic success: Complete response - 100% Recurrence rate - 0%

BCVA: Best corrected visual acuity

Of the studies comparing SP-PDT and PDT with different parameters, Reibaldi et al.[16] treated 42 eyes with chronic CSCR with SP-PDT or HF-PDT. At a mean of 12 months, they reported complete resorption of subretinal fluid in 79% of the eyes treated with SP-PDT and 91% of the eyes treated with HF-PDT. In the SP-PDT group they also observed new atrophy in the treated area on FFA in 1 eye (5%) and juxtafoveal CNV in 1 eye (5%) at 12 months post-treatment. A summary of studies on HD-PDT and HF-PDT in chronic CSCR is presented in Table 4.

In conclusion, publications on PDT in CSCR are still at the level of case series and nonrandomized comparative studies. Randomized controlled clinical trials with much larger samples are needed to evaluate the efficacy and safety of this therapy. A systematic review by Erikitola et al.[54] in 2014 evaluated results concerning SP-PDT, HD-PDT, and HF-PDT from randomized controlled studies and qualitative observational studies that met at least 70% of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria (Table 5).[55] They concluded that of various parameters, HD-PDT was the treatment option with the lowest adverse event and recurrence rates. In 4 (42.9%) of 7 studies on HD-PDT, complete resorption of subretinal fluid was observed with no recurrence in any of the eyes.[56,57,58,59] The overall recurrence rate of CSCR in the review varied between 3%-24%, though it was noted that these results were obtained from studies with small sample sizes.

Conclusion

An evaluation of the literature data regarding current treatment options for chronic CSCR, such as SML, anti-VEGF, MR antagonists, and PDT, suggests that SML is superior to CL in terms of adverse effects and comparable to PDT in terms of efficacy.

Table 4. Major studies on half-dose and half-fluence verteporfin–photodynamic therapy in central serous chorioretinopathy

Authors	Study Designdesign	Mean duration of symptoms	Number of eyes	Follow-up time	Outcome
Chan et al.[19]	Prospective, uncontrolled case series (HD-PDT)	8.2 months	48	12 months	Functional success: (mean increase in BCVA) - 51% Anatomic success: Complete response - 89.6% Recurrence rate - 8.3%
Nicolo et al.[52]	Prospective, uncontrolled case series (HD-PDT)	≥6 months	38	14.2 months	Functional success: (mean increase in BCVA) - 38% Anatomic success: Complete response - 92.1% Recurrence rate - 13.2%
Senturk et al.[53]	Prospective, uncontrolled case series (HD-PDT)	4-6 months	24	6 months	Functional success: (mean increase in BCVA) - 40% Anatomic success: Complete response - 100% Recurrence rate - 0%
Lim et al.[68]	Prospective, comparative case series (HF-PDT)	Severe hyperfluorescence group 13.2 months Mild hyperfluorescence group 11.9 months	30	6 months	Functional success: (Mean increase in BCVA) Intense hyperfluorescence group - 53% Weak hyperfluorescence group - 41% Anatomic success: Complete response Intense hyperfluorescence group - 100% Weak Hf group - 100% Recurrence rate Intense hyperfluorescence group - 0% Weak hyperfluorescence group - 7.1%
Reibaldi et al.[16]	Prospective, comparative case series (SP-PDT vs. HF-PDT)	8.5-9 months	42	SP group 8.5 months HF group 8.9 months	Functional success: (Mean increase in BCVA) SP group - 37% HF group - 65% Anatomic success: Complete response SP group - 79% HF group - 91% Recurrence rate SP group - 11% HF group - 5%

BCVA: Best corrected visual acuity, Hf: Hyperfluorescence, SP: Standard protocol, HD: Half-dose, HF: Half-fluence

Table 5. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria[47,54,55,60]		
	Item no	**Recommendation**
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Cohort study - give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study - give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study - give the eligibility criteria, and the sources and methods of selection of participants
		(b) Cohort study - for matched studies, give matching criteria and number of exposed and unexposed Case-control study - for matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) Cohort study - if applicable, explain how loss to follow-up was addressed Case-control study - if applicable, explain how matching of cases and controls was addressed Cross-sectional study - if applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses
Results		
Participants	13	(a) Report numbers of individuals at each stage of study - e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Cohort study - summarise follow-up time (e.g., average and total amount)
Outcome data	15	Cohort study - report numbers of outcome events or summary measures over time
		Case-control study - report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study - report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done - e.g., analyses of subgroups and interactions, and sensitivity analyses

Table 5 (continued)		
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Assessing the effectiveness of SML using longer-term follow-up data will provide more reliable information for comparison with the effectiveness of PDT. In addition, similar to CL, the ineffectiveness of SML in diffuse RPE leakages is considered an additional disadvantage. Although the valuable prospective randomized study by Artunay et al.[22] offered promising results, studies on anti-VEGF have usually been reports of a few cases, which limits the power of these studies. Therefore, performing randomized studies with larger sample sizes will yield more reliable results. Moreover, the most probable pathogenesis of the disease is not closely related to the mechanism of action of anti-VEGF, which suggests that these agents may not be very effective. Studies on MR antagonists have shown that these are effective treatment options; however, the results indicate that these short acting agents are more disadvantageous in terms of patient compliance and in comparison with treatment options with more permanent effects such as PDT and SML. Studies with longer follow-up will also provide more definitive data regarding the effectiveness of MR antagonists. Finally, although PDT is known to be more costly than CL, studies indicate that verteporfin PDT is superior to and safer than CL therapy in terms of effectiveness and adverse event profiles, particularly in chronic, subfoveal, and juxtafoveal involvement. In particular, the fact that PDT at different parameters (HD-PDT, HF-PDT) minimized adverse effects such as choroidal ischemia and CNV supports this treatment as an effective and safe treatment option for chronic CSCR.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Samet Gülkaş, Özlem Şahin, Concept: Samet Gülkaş, Özlem Şahin, Design: Özlem Şahin, Data Collection or Processing: Samet Gülkaş, Analysis or Interpretation: Samet Gülkaş, Özlem Şahin, Literature Search: Samet Gülkaş, Writing: Samet Gülkaş.

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Case Report

Central Serous Chorioretinopathy: A Complication Associated with Behçet's Disease Treatment

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Abstract

Central serous chorioretinopathy (CSCR) is characterized by a well-defined serous choroidal detachment of the retinal pigment epithelium with one or more focal lesions of the neurosensory retina. Risk factors for CSCR are psychosocial stress, increased endogenous catecholamine, and increased endogenous cortisol. Systemic steroids can cause ocular side effects such as cataract development, increased intraocular pressure, and less frequently the development of CSCR, which can resolve spontaneously with close follow-up and simple treatment modification. CSCR should be considered in patients who complain of worsening vision under steroid treatment for pathologies requiring steroid therapy. In this study we present two patients, one man and one woman, who developed acute CSCR while under systemic steroid treatment for Behçet's disease.

Keywords: Behçet's disease, central serous chorioretinopathy, steroid

Introduction

Behçet's disease is a multisystemic condition of unknown etiology characterized by chronic, recurrent vasculitis. Ocular and systemic complications can be prevented by controlling the disease with early and effective treatment. Systemic steroids and immunomodulatory agents play an important role in controlling inflammation. Long-term steroid use can lead to systemic side effects such as osteoporosis, predisposition to infection, intestinal ulcers, hyperglycemia, and exacerbated hypertension, as well as severe ocular side effects such as cataract, elevated intraocular pressure and, less frequently, central serous chorioretinopathy (CSCR).[1]

CSCR is characterized by well-defined serous detachment of the neurosensory retina at the macula that may be accompanied by retinal pigment epithelium (RPE) detachment.[2,3] The pathogenesis is believed to involve choroidal hyperperfusion and RPE barrier dysfunction. Different forms of steroid treatment, such as oral, inhaled, intranasal, intravitreal, and epidural, can cause CSCR.[4] Here we present two cases, one woman and one man, who developed acute CSCR while under systemic steroid therapy for Behçet's disease.

Case Reports

Case 1

A 44-year-old woman with Behçet's disease presented to the Uvea and Behçet's Department of our center complaining of reduced vision in her left eye. Ophthalmologic examination showed her visual acuity was decreased from 1.0 in both eyes to 0.9/0.7 (decimal). Optical coherence tomography (OCT) revealed typical lesions consistent with CSCR in both eyes (Figure 1a). Fundus fluorescein angiography (FFA) showed focal areas of leakage from the RPE into the subretinal space in both eyes (Figure 2). The patient was taking 40 mg/day methylprednisolone, 100 mg/day azathioprine, and 40 mg/day pantoprazole as treatment for Behçet's disease. She also described panic attack-like symptoms and was referred to the psychiatry department to begin antidepressant therapy. During this time a gradual reduction of her oral steroid dose was planned and

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antidepressant therapy was initiated. On day 20 of the tapering schedule, her dose of oral methylprednisolone was 32 mg/day and her visual acuity had returned to 1.0 despite persistent bilateral CSCR findings in OCT. On day 90 of the tapering schedule, oral methylprednisolone dose was 16 mg/day, visual acuity remained 1.0 bilaterally, and OCT showed the subfoveal fluid had complete resolved in the right eye but improved only partially in the left eye. Treatment with nepafenac drops 4 times daily was started in the left eye. At 6 months, oral steroid was maintained at 8 mg/day; there were no remaining signs of bilateral serous detachment (Figure 1b) and the patient had full vision in both eyes. No recurrence has been observed during 14 months of follow-up.

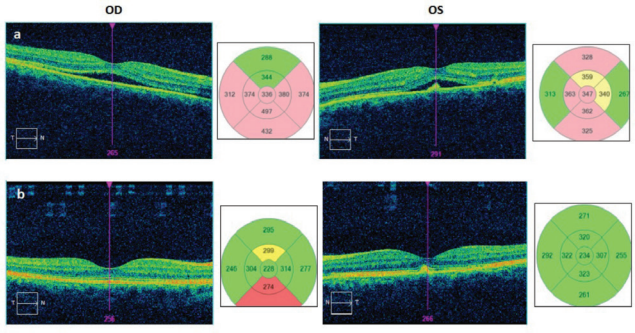

Figure 1. a) Optical coherence tomography shows hyporeflective serous detachment between the subfoveal neurosensorial retina and retinal pigment epithelium in the right and left eyes. In the left eye there is also hyperreflectivity consistent with subfoveal scar associated with serous detachment, b) With steroid tapering, the subfoveal fluid was completely resorbed in both eyes at 6 months, but hyperreflectivity consistent with subfoveal retinal pigment epithelium scar persisted in the left eye

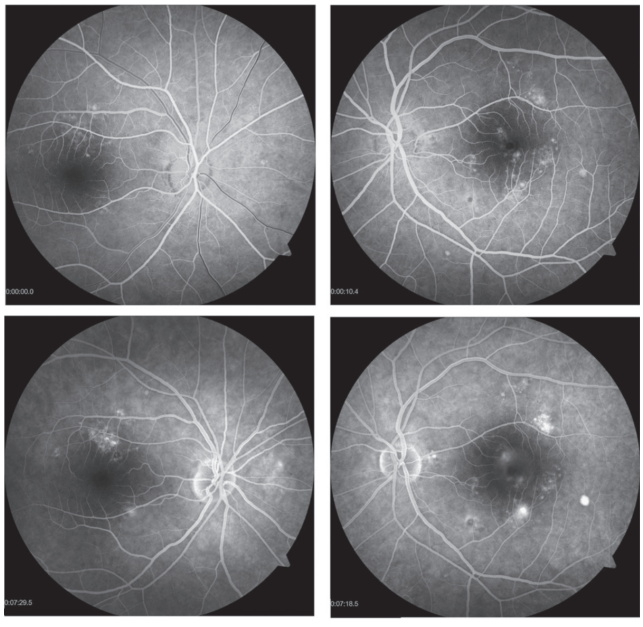

Figure 2. Fundus fluorescein angiography shows multiple focal areas of leakage from the retinal pigment epithelium into the subretinal space in both eyes and macular edema in the left eye

Case 2

A 37-year-old man with Behçet's disease presented to our clinic with complaints of decreased vision in his left eye. Visual acuity was 1.0/0.6 and anterior segment examination was normal. No pathology was detected on fundus examination in the right eye, while macular OCT showed a typical lesion consistent with CSCR in the left eye (Figure 3a). Increasing hyperfluorescence with smoke-stack pattern was observed in the left macula on FFA (Figure 4). While taking a detailed history, the patient stated he had been prescribed oral methylprednisolone 40 mg/day in the rheumatology department due to arthritis of the left ankle secondary to Behçet's disease. The patient was referred to the rheumatology department for steroid dose reduction and the psychiatry department due to a stressed psychological state. He was started on oral diazomide 500 mg twice daily and nepafenac drops 4 times daily in the left eye. On day 40 of the steroid tapering schedule, oral methylprednisolone dose was 12 mg/day,

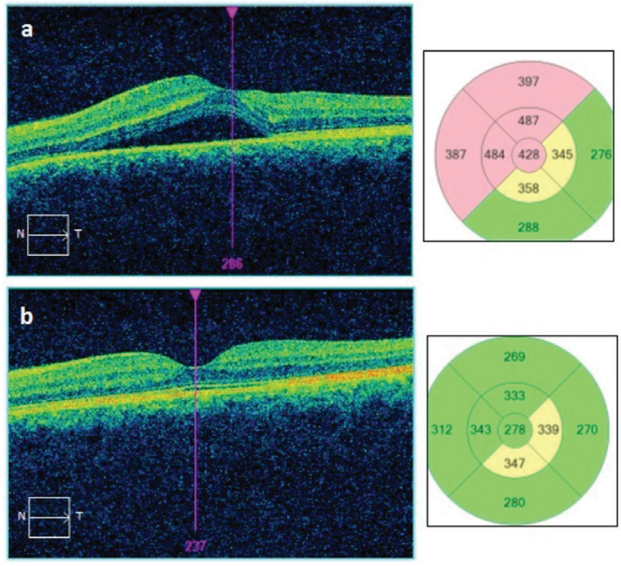

Figure 3. a) Optical coherence tomography revealed a large amount of hyporeflective subfoveal fluid between the neurosensorial retina and retinal pigment epithelium extending superonasally from the subfoveal area, b) OCT taken at month 4 of a steroid tapering schedule showed complete resolution of the serous detachment with no damage to the retinal layers

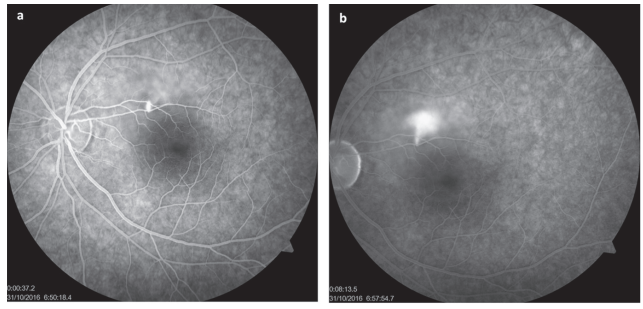

Figure 4. Fundus fluorescein angiography imaging showed a smoke-stack pattern of hyperfluorescence in the superior region of the left macula characteristic of Central serous chorioretinopathy starting in the early phase (a) and increasing in the late phase (b)

visual acuity was improved to 0.7, and OCT showed a significant reduction in subfoveal fluid in the left eye. At 4 months, the methylprednisolone dose was 6 mg/day, his vision was 0.8, and the subfoveal fluid was completely resorbed (Figure 3b). The patient was followed for 16 months. In his final examination, ocular findings were normal with no signs of recurrence.

Discussion

CSCR commonly affects young/middle-aged men aged 25-55 years and is often unilateral and reversible. About 40% of patients have bilateral disease, though this rate is higher among patients with chronic CSCR.[5] Similarly, our patients were 44 and 37 years old and represented both sexes. Only the first patient had bilateral CSCR. The primary symptom of CSCR is sudden blurred vision due to fluid leakage and serous detachment in the macula. Metamorphopsia, micropsia, central scotoma, or impaired color vision may also occur.

Risk factors include psychosocial stress, elevated endogenous catecholamine, hypertension, pregnancy, organ transplantation, and obstructive sleep apnea.[6] Because psychosocial stress was identified as a risk factor in our patients, psychiatric consultation was requested for both of them. Corticosteroids are another important risk factor in the development of CSCR.[7,8] Steroid use is believed to increase the permeability of choroid capillaries and RPE by inhibiting collagen synthesis and disrupting ion pump function.[9,10] Glucocorticoids are also known to alter blood-aqueous barrier permeability and disrupt the external blood-retinal barrier by increasing cAMP levels in RPE cells.[11] Steroids administered by various routes (oral, inhaled, intranasal, intravitreal, epidural) contribute to the development CSCR.[4,12] In addition, the literature includes reports of a patient under systemic steroid therapy for "retrobulbar neuritis" developing multiple areas of serous retinal detachment in both eyes and a patient misdiagnosed with Vogt-Koyanagi-Harada disease and treated with corticosteroids who actually had atypical bullous CSCR.[13,14] Both of our patients were receiving oral steroid therapy for Behçet's disease when they presented with CSCR.

Visual prognosis is generally very good in CSCR and follow-up alone is recommended if there is no underlying pathology. Most patients show spontaneous resolution within 3-4 months.[15] Patients with steroid-associated CSCR should be followed with their steroid dosage reduced as low as permitted by their disease. In these patients, as in our 2 cases, clinical findings return to normal within a few months, resulting in good visual improvement. The rate of spontaneous resolution is higher in steroid-related cases than with other CSCR etiologies.[16] Photodynamic therapy (PDT) is a treatment approach commonly used for patients who do not show spontaneous resolution within 3 months, have bilateral or recurrent disease, or who require rapid visual rehabilitation.[17] However, the effectiveness of PDT may vary for steroid-associated CSCR.[8] Furthermore, a meta-analysis evaluating the efficacy of anti-vascular endothelial growth factor (anti-VEGF) therapy in CSCR showed that anti-VEGF therapy was not superior to observation at 6-month follow-up in acute cases in which persistent subretinal fluid did not last longer than 3 months.[18] In an evaluation of comparative studies of chronic cases, however, anti-VEGF therapy was not superior to observation in terms of best corrected visual acuity (BCVA), but there were significant differences between the two groups in terms of central macular thickness (CMT).[18] In the same meta-analysis, it was reported that non-comparative studies demonstrated significant differences in BCVA and CMT after anti-VEGF therapy at 1, 6, and 12 months follow-up.[18] Although results have been controversial, intravitreal anti-VEGF injection may be beneficial in chronic CSCR by reducing choroidal vascular hyperpermeability and obstruction.[19] Both of our patients showed spontaneous resolution.

In conclusion, not only uveitis but also non-uveitic pathologies such as CSCR should be considered when patients present with reduced vision while taking steroids for pathologies such as Behçet's disease that require steroid therapy. Otherwise, CSCR cases exhibiting atypical clinical features may be difficult to diagnose. CSCR can resolve spontaneously with close follow-up and simple treatment modifications.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Melike Balıkoğlu Yılmaz, Concept: Melike Balıkoğlu Yılmaz, Design: Melike Balıkoğlu Yılmaz, Nur Doğanay, Data Collection or Processing: Melike Balıkoğlu Yılmaz, Nur Doğanay, Betül Orduyılmaz, Analysis or Interpretation: Melike Balıkoğlu Yılmaz, Nur Doğanay, Erdinç Aydın, Ali Osman Saatçi, Literature Search: Melike Balıkoğlu Yılmaz, Nur Doğanay, Writing: Melike Balıkoğlu Yılmaz, Nur Doğanay.

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Case Report

Staphylococcus epidermidis Endophthalmitis Masquerading as Panuveitis After an Imperceptible Ocular Trauma

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Abstract

Endophthalmitis after a penetrating trauma occurs in 3% to 30% of cases. Prompt recognition and treatment are paramount to avoid irreversible visual loss. We present a case of severe panuveitis following ocular trauma with a tree branch that did not cause any evident ocular wound and discuss the difficulties in achieving a diagnosis that can allow proper treatment. A healthy 21-year-old man presented with acute anterior uveitis. He was managed elsewhere with oral acyclovir and topical steroids for presumed herpetic uveitis. He subsequently developed severe panuveitis with profound decrease in vision. Diagnostic vitrectomy was performed and vitreous samples were positive for *Staphylococcus epidermidis*. Systemic and intravitreal antibiotic therapy was initiated and after 5 days, the patient recovered with a remarkable improvement in visual acuity to 6/12. Post-traumatic endophthalmitis can result from an imperceptible trauma with no obvious compromise of the globe.

Keywords: Diagnostic vitrectomy, exogenous endophthalmitis, staphylococcus epidermidis, ocular trauma, penetration trauma

Introduction

Endophthalmitis is a microorganismal infection caused exclusively by bacteria or fungi within the structures of the eye, including the aqueous and vitreous humor. Most cases are caused by microbial inoculation from an exogenous source, usually after blunt or penetrating trauma, surgery, foreign body, or as a complication of an eye infection such as keratitis or conjunctivitis. Bacterial infection is the most common type and the clinical presentation is typically acute. Acute bacterial endophthalmitis is a serious sight-threatening condition that must be addressed as an emergency. Endophthalmitis consequent to penetrating eye trauma has been reported in 3% to 30% of the cases.[1,2]

We present the case of a healthy young male who developed serious acute *Staphylococcus epidermidis* endophthalmitis following an imperceptible trauma that did not overtly compromise the integrity of the eye globe.

Case Report

A healthy 21-year-old man was admitted to our hospital after being referred from another medical institution because of worsening left eye (LE) uveitis. He was treated 3 weeks earlier with oral acyclovir and topical steroids because of suspected LE herpetic anterior uveitis as serological tests revealed positive immunoglobulin M to herpes simplex virus-1. Initially he responded to treatment but 2 weeks later, his vision declined from 6/9 to counting fingers (CF), resulting in his referral to our center.

The patient denied any relevant past medical history. However, he mentioned that a month earlier he was examined for LE discomfort and diagnosed with allergic conjunctivitis following minor blunt trauma from a tree branch.

On examination, visual acuity (VA) was 6/6 in the right eye (RE) and CF at 1 meter in the LE. Intraocular pressure was 14 mmHg in both eyes. RE anterior and posterior segments were normal. There was a remarkable LE anterior chamber reaction

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with dust-like keratic precipitates, cells (4+), flare (2+), and some iris nodules. Fundus assessment was not possible because of dense vitritis. B-scan and high-frequency ultrasound did not reveal any intraocular foreign body. Aqueous tap was performed and the sample was sent for culture and polymerase chain reaction analysis. It was negative for all herpes viruses and for 16S rDNA. Meanwhile, with oral steroids and valacyclovir, the patient showed signs of improvement and LE VA improved to 6/15. Despite the remarkable improvement, it was insufficient as the patient continued to have marked anterior uveitis and vitritis. A white shadow was noted in the peripheral temporal retina of the LE which again could not be assessed properly due to vitreous opacities (Figure 1). The patient eventually underwent pars plana vitrectomy and laser retinopexy was performed around the white peripheral temporal lesion, which was later believed to be the site of penetrating injury by a thorn on the tree branch from the previous trauma described by the patient. Gram staining of the undiluted vitreous samples showed gram-positive cocci. 16S rDNA was positive for *S. epidermidis*, and blood agar and chocolate agar cultures confirmed the result with moderate growth.

The patient was treated with intravitreal antibiotics (vancomycin 1 mg/0.1 mL and ceftazidime 2.25 mg/0.1 mL) and intravitreal dexamethasone 400 mcg/0.1 mL as well as intravenous (IV) vancomycin (1 g twice/day), and oral prednisone was continued.

After 48 hours of treatment, the patient showed remarkable clinical improvement. LE VA was 6/12. There was no need to administer more intravitreal antibiotics.

After 5 days of IV antibiotic treatment, the patient was discharged on topical and a tapering regimen of oral steroids.

After a follow-up period of 3 months, LE VA was 6/6 with complete resolution of the infectious process (Figure 2).

Discussion

The normal bacterial flora of the human body is composed of gram-positive and gram-negative microorganisms, primarily *S. epidermidis* and *Propionibacterium acnes*, which are isolated under normal conditions from the skin, eyelid margins, conjunctival sac, and mucosal tissues.[3]

S. epidermidis is the most representative of this bacterial flora since it is commonly found in ocular surface isolates.[4] In our patient's case, this microorganism was able to initiate and perpetuate the inflammatory response via a traumatic mechanism that allowed it to colonize the vitreous cavity and retina. The peripheral retinal temporal scar appeared to be the site of injury from a fine thorn that inoculated the bacteria, subsequently leading to severe endophthalmitis.

Sabaci et al.[2] reported in a retrospective study of 228 eyes with deadly-weapon-related open-globe injuries that *S. epidermidis* was the most common isolate and that infection with this less virulent microbe was the only factor associated with favorable outcome in their series. Our patient sustained a minor, imperceptible trauma without any evidence of penetrating intraocular foreign body on biomicroscopic examination, thus complicating the clinical picture.

Risk factors for the development of post-traumatic endophthalmitis have been examined by several groups. Essex et al.[5] analyzed the clinical course and visual outcomes of 250 consecutive patients admitted to a single ophthalmic hospital with open-globe injuries. The following factors were associated with the subsequent development of endophthalmitis: dirty wound, retained intraocular foreign body (IOFB), lens capsule breach, delayed primary repair, and residing in a rural area.

In the case of our patient, the injury likely occurred in a rural setting, but there was no lens capsule rupture or delayed repair of the inciting wound because it was most probably a self-sealing wound that did not lead to clinically visible signs.

The use of systemic and intraocular antibiotics for prophylaxis against post-traumatic endophthalmitis remains controversial. Nevertheless, when systemic antibiotics are not employed after open-globe injuries, there is a greater risk for endophthalmitis development.[6] In a prospective, randomized study, cases of IOFB that were managed with intracameral and intravitreal antibiotics were associated with a reduced risk of endophthalmitis compared with the control group treated with intravitreal balanced salt solution.[2]

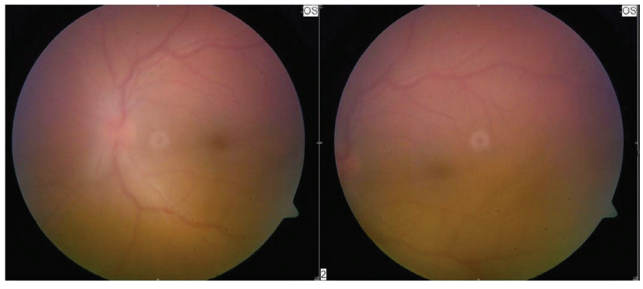

Figure 1. Color fundus photograph of the left eye showing hazy fundus view because of dense vitritis

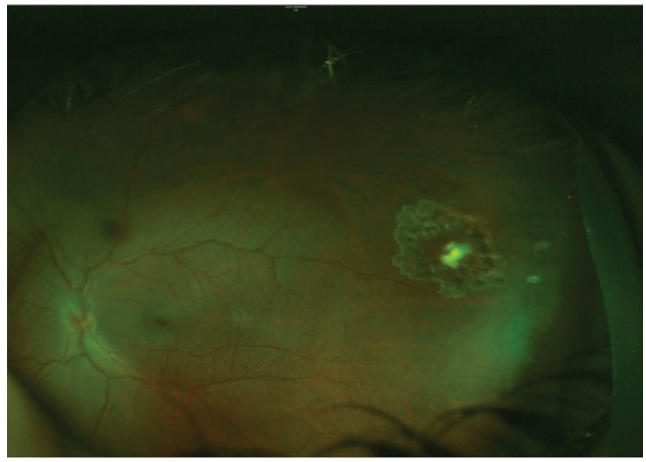

Figure 2. Color fundus photograph of the left eye 2 weeks postoperatively showing a clear fundus view (binocular indirect ophthalmoscopy score of zero) with normal-looking optic disc, macula, and retinal vessels. However, a white scar surrounded by laser marks is visible in the temporal peripheral retina, indicating the site of the penetrating injury

In conclusion, this case illustrates that post-traumatic endophthalmitis can occur with an imperceptible trauma without obvious compromise of the globe. Thorough clinical history is needed in order to properly assess subtle signs and ensure a satisfactory outcome.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Juan Martin Sanchez, Diego Almeida, Tareq Jaouni, Radgonde Amer, Design: Juan Martin Sanchez, Diego Almeida, Tareq Jaouni, Radgonde Amer, Data Collection or Processing: Juan Martin Sanchez, Diego Almeida, Tareq Jaouni, Radgonde Amer, Analysis or Interpretation: Juan Martin Sanchez, Diego Almeida, Tareq Jaouni, Radgonde Amer, Literature Search: Juan Martin Sanchez, Diego Almeida, Tareq Jaouni, Radgonde Amer, Writing: Juan Martin Sanchez, Diego Almeida, Tareq Jaouni, Radgonde Amer.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

Periorbital Emphysema After Endoscopic Nasal Polyp Surgery

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Abstract

Periorbital and subcutaneous emphysema after transnasal endoscopic surgery are rare. Periorbital emphysema has been reported after facial trauma, dental interventions, procedures such as endoscopic sinus surgery and rhinoplasty, and due to medications such as systemic steroids. Although very rare, it may require urgent intervention because of the risk of increased intraocular pressure and impaired blood supply to the globe. The otolaryngology department requested ophthalmology consultation for a 65-year-old male patient who had severe periorbital emphysema of the right eye the day after endoscopic nasal polypectomy due to severe coughing and straining. Crepitus was detected on skin palpation and immediate intervention was performed by passing a 21-gauge needle through the skin into the subcutaneous tissue of the upper and lower eyelids to evacuate the subcutaneous air. The patient's clinical symptoms resolved with no postoperative complications.

Keywords: Endoscopic surgeries, periorbital emphysema, valsalva maneuver

Introduction

Periorbital emphysema is a clinical condition characterized by the accumulation of air beneath the skin around the orbit after surgery. It has been reported after maxillofacial surgeries, dental interventions, endoscopic sinus surgeries, and procedures such as rhinoplasty.[1,2,3,4] Although periorbital emphysema is rare, it can lead to conditions that require urgent decompression. In this case report, a patient with periorbital emphysema was evaluated.

Case Report

A 65-year-old man was referred by the otolaryngology department to our outpatient clinic due to sudden swelling and mild pain around the right eye. On examination, the patient exhibited what appeared to be severe edema encompassing the upper and lower lids of the right eye (Figure 1). Crepitus was clearly audible on palpation of the eyelids. An attempt to open the lids was unsuccessful. Visual acuity and intraocular pressure could not be measured due to extreme lid swelling. The patient reported that he had undergone transnasal endoscopic nasal polypectomy through the right nostril 2 days earlier. He said he had been instructed not to cough or strain after the endoscopic nasal surgery and the sudden swelling occurred immediately after severe coughing and straining. We suspected that the sinus wall was weakened due to his endoscopic surgery and the increased pressure caused by straining had forced air in the nose into the periorbital area. B-mode ultrasonography showed trapped air in the periorbital area (Figure 2).

Considering the patient's anxiety, the severity of periorbital emphysema, inability to conduct a full ophthalmologic examination, and the risk of complications such as compressive optic neuropathy, the patient was re-evaluated for a surgical intervention. After consultation, it was decided to evacuate the air using a 21 gauge needle inserted in the subcutaneous tissue of the upper and lower lids. In sterile conditions, the eye area was cleaned with 10% povidone-iodine. A 21-gauge needle was passed through the skin and subcutaneous tissue of the upper and lower lids parallel to the tarsus about 1.5 cm from the

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lid margin. Evacuation of subcutaneous air was evident from a significant reduction in lid swelling during the procedure (Figure 3). The patient's vital signs were stable and the procedure was concluded. He was discharged with systemic antibiotics (cefuroxime axetil 500 mg twice daily) and moxifloxacin drops four times daily.

On follow-up examination the next day, the periorbital emphysema was substantially reduced and the globe could be examined (Figures 4, 5). He had full visual acuity in both eyes; intraocular pressure was 17 mmHg in the right eye and 16 mmHg in the left eye. Dilated fundus examination was normal. No restriction in eye movements was observed. Follow-up examinations at 1 week and 1 month revealed no pathological findings.

Discussion

Trapped air in the periorbital subcutaneous tissue has been described in the literature using various terms such as subcutaneous emphysema, surgical emphysema, and interstitial emphysema.[5,6,7] Although periorbital emphysema is usually associated with surgery, infection, or traumatic orbital wall fractures, spontaneous cases and other causes such as heavy lifting have also been reported. One of these reports described a 23-year-old male who developed periorbital emphysema in his left eye while lifting weights at a gym. No orbital wall fracture was detected on computed tomography and the periorbital emphysema regressed after 7 days with antibiotic and non-steroidal anti-inflammatory treatment.[8]

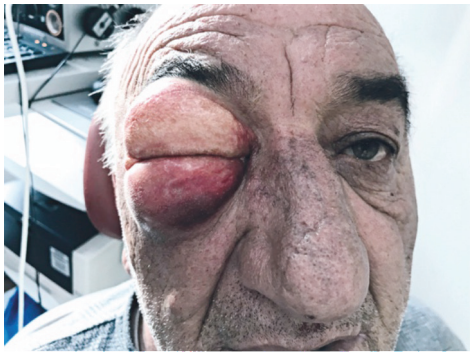

Figure 1. Periorbital emphysema involving the upper and lower eyelids of the right eye

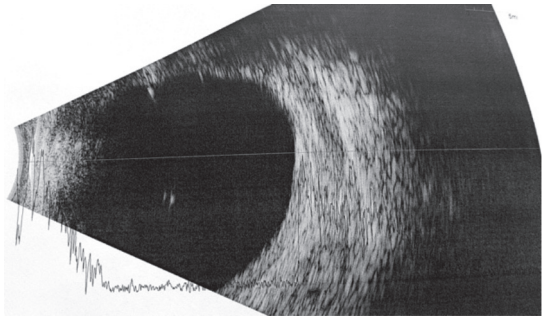

Figure 2. B-mode ultrasonography before surgical intervention

Periorbital emphysema is an uncommon clinical presentation that usually does not lead to major problems or require surgical decompression; however, in rare cases surgical decompression may be considered due to the potential for increased intraocular pressure and impaired ocular perfusion.[9] In addition, it is important to differentiate periorbital emphysema from conditions like angioedema, anaphylactic reaction, and orbital cellulitis in order to avoid unnecessary antibiotic and antihistaminic treatment. In one case report, a patient developed swelling around the left eye after undergoing a dental procedure under local anesthesia. It was mistaken for an allergic reaction to the local anesthetic and the patient was discharged with antihistaminic therapy. However, she returned 6 hours later unable to open her eye and was found to have emphysema of the face and neck.[10] Crepitus caused by air bubbles in the subcutaneous tissue is an important differential finding.[11] Normal body and skin temperature and mild or absent pain are important in the differential diagnosis

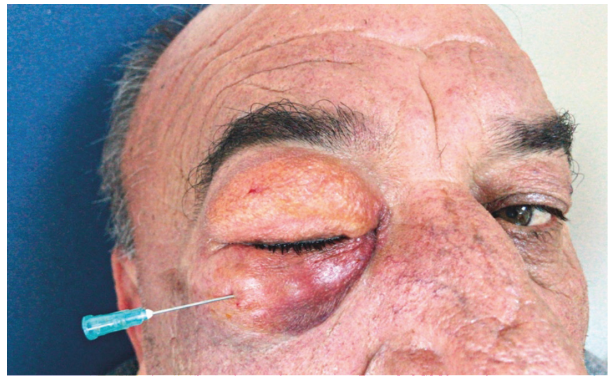

Figure 3. Marked reduction in lid swelling 5 minutes after surgical intervention

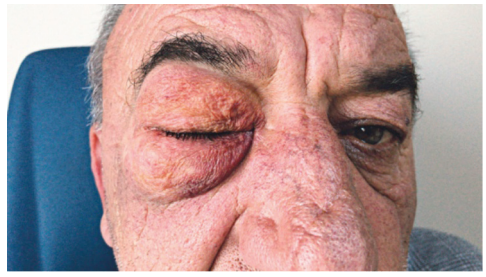

Figure 4. Appearance 1 day after surgical intervention

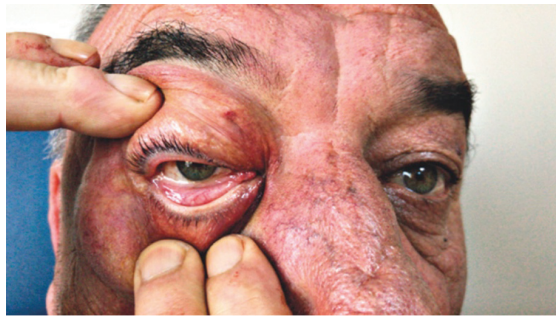

Figure 5. Appearance 1 day after surgical intervention

with orbital cellulitis. Our patient had pronounced crepitus and normal skin temperature. Imaging of the periorbital structures is also important for differential diagnosis. B-mode ultrasonography demonstrated trapped air in our case. Magnetic resonance imaging or computed tomography of the orbit can also be used to visualize emphysema.[12]

The use of systemic antibiotics in these patients is controversial. The general opinion is that systemic antibiotic prophylaxis is necessary in cases associated with oral or nasal surgery due to concern that staphylococci, streptococci, and anaerobic bacteria introduced via the same route as the emphysema (through a compromised bony wall) may cause periorbital infection.[13] For this purpose we treated our patient with cefuroxime axetil, an oral cephalosporin with good soft tissue penetration.

A symptomatic approach is preferred for treatment. Painkillers can be given if there is pain, and local or systemic antibiotic therapy can be used if there are signs of infection. The condition tends to resolve within a week, but life-threatening conditions such as cardiopulmonary embolism, cardiac tamponade, and respiratory distress may occur depending on the amount of air and the deep fascial plane where it is trapped.[14] Our patient displayed much more severe periorbital emphysema compared to images of other patients reported in the literature. This combined with his anxiety and diabetes led to our decision to perform urgent surgical intervention in order to reduce the risk of embolism. Although we believe that this decision was appropriate in this case to provide more rapid clinical improvement, eliminate pressure on the globe, and reduce the risk of embolism, we believe similar cases can be followed with a nonsurgical, symptomatic approach.

Periorbital emphysema has been reported after maxillofacial surgeries, dental interventions, and endoscopic sinus surgeries.[1,2,3,15] Generally, air in the nasal cavity leaks into the periorbital space through a path in the deep orbital structures resulting from weakness or fracture in the bony structures due to surgical trauma.[16] When questioned, our patient said he had also previously undergone endoscopic sinus surgery and nasal polyp surgery, both by transnasal approach. After these two previous endoscopic surgeries, the third operation may have caused weakness in the sinuses and bony structures of the nasal wall. We believe that when the patient increased the intranasal pressure with severe coughing and straining, air was forced through these weak tissues and into the periorbital area. In a study evaluating 137 cases of periorbital edema, it was reported that periorbital emphysema was more common in surgical procedures involving the orbital medial wall (78%).[17] Because ultrasound clearly demonstrated the air trapped in the periorbital area in our patient, no additional imaging was performed. In a study of 1658 patients who had endoscopic sinus surgery, the incidence of ophthalmologic complications was 0.66%, with the most common being periorbital ecchymosis with or without periorbital emphysema (0.3%). The main risk factors to which the authors attributed complications were extension of primary disease, previous surgery, and anticoagulant therapy.[18]

Periorbital emphysema can also occur after ocular surgeries. Globe perforation, deep orbital tissue damage, and subsequent periorbital edema have been reported during retrobulbar anesthesia in particular.[19] The possibility of globe perforation should not be overlooked in patients who have undergone intraocular surgery.

Although periorbital emphysema usually resolves within a few days with follow-up or decompression, a fatal case of emphysema starting in the periorbital area after routine gastrointestinal endoscopy and progressing to the face, neck, and chest with no ocular findings of compression was reported.[20]

Periorbital emphysema may be a rapidly progressive and life-threatening complication, or a benign and spontaneously resolving clinical entity. Definitive diagnosis should be established quickly and, after evaluating the potential risks, the patient can either be managed with observation and symptomatic treatment or with a simple surgical intervention, as in this case.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Murat Fece, Concept: Esat Çınar, Dizayn: Esat Çınar, Design: Esat Çınar, Data Collection or Processing: Esat Çınar, Cem Küçükerdönmez, Analysis or Interpretation: Esat Çınar, Cem Küçükerdönmez, Literature Search: Esat Çınar, Berna Yüce, Writing: Esat Çınar, Berna Yüce.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report

Pneumatic Displacement of a Dense Sub-inner Limiting Membrane Pre-macular Hemorrhage in Dengue Maculopathy: A Novel Treatment Approach

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Abstract

Sub-inner limiting membrane (ILM) hemorrhage is a rare presenting feature of dengue maculopathy. A 24-year-old man in active military service who was recently treated for dengue hemorrhagic fever presented with sub-ILM bleeding in right eye (dominant eye) with profound diminution of vision. Spectral domain optical coherence tomography and fundus fluorescein angiography confirmed sub-ILM hemorrhage with no evidence of vasculitis/venous occlusion or neovascularization. He refused active surgical management by pars plana vitrectomy and was treated with pneumatic tamponade of C3F8 (100%) gas with prone positioning in order to achieve faster visual recovery. He responded well to treatment with complete visual recovery in 1 week. This case report documents for the first time treatment of sub-ILM hemorrhage in the premacular area with pneumatic tamponade in prone position leading to rapid and complete visual recovery in a patient with dengue maculopathy. This novel approach can be employed for patients who are ineligible for more active surgical management.

Keywords: Dengue maculopathy, sub-ILM hemorrhage, pneumatic displacement

Introduction

Dengue fever is an acute viral infection caused by four closely related dengue viruses (Flavivirus) and transmitted through the bite of infected female *Aedes aegypti* mosquitos.[1] Clinical manifestations of dengue fever range from benign self-limiting fever, chills, and headache to severe dengue hemorrhagic fever and dengue shock syndrome.[2] Dengue maculopathy may develop in patients with dengue fever. Common ocular manifestations include retinal hemorrhages, macular edema, yellow spots, optic disc swelling, and retinal vasculitis.[3,4,5] Marked thrombocytopenia in dengue fever may predispose to severe forms of ocular disease and may present with premacular hemorrhages in rare cases.[6]

There is no proven antiviral treatment or commercially available vaccine for both dengue fever and dengue maculopathy.[7] The use of steroids has been reported in some cases with variable response. However, good visual outcome may also be the natural course of the disease. Certain professionals with premacular hemorrhage complicating dengue maculopathy will require rapid visual recovery which may not be possible by using steroids or letting the disease take its natural course. We report a case of successful treatment of dense sub-ILM premacular hemorrhage in dengue maculopathy with pneumatic displacement using C3F8 gas in an active military personnel requiring early recovery of vision. In this case we used a novel technique of C3F8 pneumatic tamponade and prone positioning to displace dense sub-ILM hemorrhage with minimal intervention to avoid the potential risk of pars plana vitrectomy surgery in a young patient.

Case Report

A 24-year-old male active military personnel presented with complaints of profound diminution of vision in his right (dominant) eye of 5 days duration. He had been diagnosed with dengue hemorrhagic fever about 20 days earlier, treated with supportive therapy only without any blood/blood component

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infusion, and discharged from hospital 10 days earlier. During hospitalization, his lowest platelet count was 40,000 per microliter of blood without any ocular symptoms. On initial examination, his best corrected visual acuity Best-corrected distance visual acuity was 20/400 in right eye and 20/20 in left eye. Anterior segment examination in both eyes was normal. Fundus examination in the right eye revealed premacular hemorrhage about 2 disc diameters (DD) in size occupying the central macula and obscuring underlying details due to a splinter hemorrhage at the superonasal aspect of the disc (Figure 1). There was no evidence of any vasculitis or venous occlusion. Optical coherence tomography (SD-OCT) revealed hemorrhage to be occupying the sub-ILM space, obscuring deeper foveal details (Figure 2). Fundus fluorescein angiography showed blocked fluorescence due to blood in the sub-ILM space, with no evidence of vasculitis or foveolitis. His present systemic work-up was normal and platelet counts revealed mild thrombocytopenia (120,000 per microliter of blood).

The patient was informed and counseled about different treatment approaches including "wait-and-watch" for spontaneous recovery, pars plana vitrectomy, and a novel technique of pneumatic displacement with intraocular gas tamponade. The patient did not consent to active surgical management by pars plana vitrectomy. Being in active military service with dominant eye involvement, rapid recovery was warranted, so he was treated with 0.3 ml of C3F8 (100%) injected intravitreally in aseptic conditions followed by paracentesis in the operating theatre with prone positioning (Figure 3). He responded well to treatment with partial displacement and absorption of sub-ILM blood by day 3 post-C3F8 injection (Figure 4) and complete clearing of sub-ILM blood by the end of the first week (Figure 5). OCT showed normal foveal contour with remnants of ILM (Figure 6) seen over the macula with recovery of vision to 20/20 without any metamorphopsia or scotoma.

Discussion

Dengue maculopathy is the presence of macular swelling, hemorrhages, and yellow spots in the macula due to retinal or choroidal vasculopathy. It can present as macular edema (76.9%), macular hemorrhage (69.2%), foveolitis (28-33.7%), vasculitis, or vascular occlusion.[8] Other less common dengue-related ocular signs include vitreous hemorrhage and rarely premacular hemorrhages, as seen in our case.[9] Dengue-related ocular disease is often self-limiting and resolves spontaneously without treatment in 6-8 weeks. Patients with intraretinal vascular or choroidal leakage, signs of active ocular inflammation, and foveal swelling are more likely to benefit from steroid therapy.[10] Larger studies are needed to validate and justify its usage, as corticosteroid therapy does come with its own side effects.

The prolonged presence of sub-ILM blood as seen in our case may lead to the development of significant epiretinal tissue proliferation with significant visual loss and ocular morbidity.[11] While pars plana vitrectomy likely has the greatest anatomic success rate, the well-known complications limit immediate use in the majority of situations.[12] Nd:YAG laser hyaloidotomy is another noninvasive method which enables drainage of extensive premacular subhyaloid hemorrhage into the vitreous, facilitates absorption of blood cells, and improves vision within days by clearance of the obstructed macular area.[13] It has been advocated that hemorrhage less than 3 DD in size should not be subjected to photodisruptive laser for safety reasons. This size

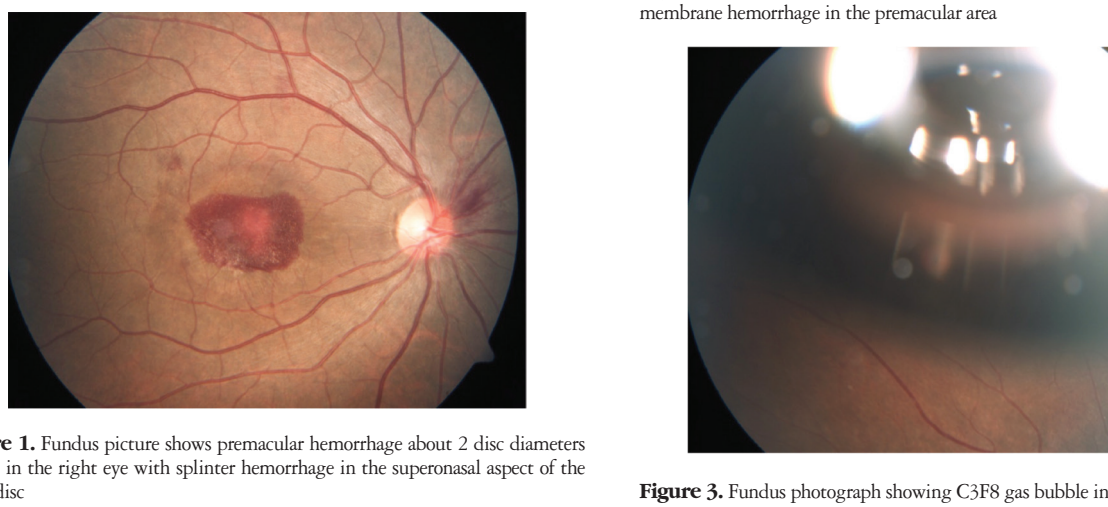

Figure 2. Optical coherence tomography of patient confirming sub-inner limiting membrane hemorrhage in the premacular area

Figure 1. Fundus picture shows premacular hemorrhage about 2 disc diameters in size in the right eye with splinter hemorrhage in the superonasal aspect of the optic disc

Figure 3. Fundus photograph showing C3F8 gas bubble in the vitreous cavity

helps to increase the cushion effect of the hemorrhage in order to avoid inadvertent retinal damage by the photodisruptive laser.[14] Iatrogenic foveal or parafoveal macular can also be a potential complication of this procedure.[15] Our patient was active military personnel with right eye (firing eye) involvement and 2 DD premacular hemorrhage who required rapid visual recovery with no residual visual morbidity, so management with pneumatic displacement was preferred. He underwent minimally invasive intervention in the form of C3F8 tamponade with prone positioning, enabling full visual recovery within 7 days post-intervention. There were no sequelae such as metamorphopsia and persistent central or paracentral scotoma, which were reported in up to 59.5% of 74 affected eyes at 2-year follow-up in a study by Teoh et al.[16]

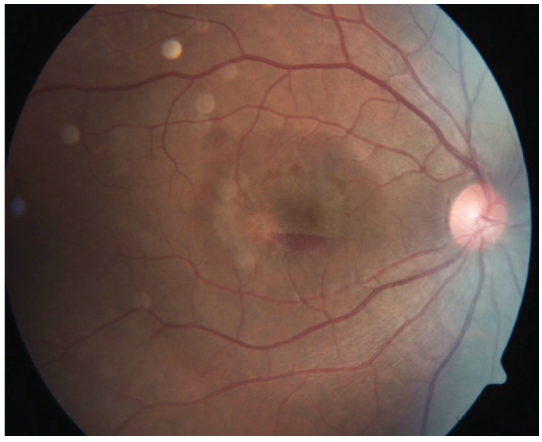

Figure 4. Fundus photograph 3 days post-C3F8 tamponade showing substantial clearing of sub-inner limiting membrane hemorrhage

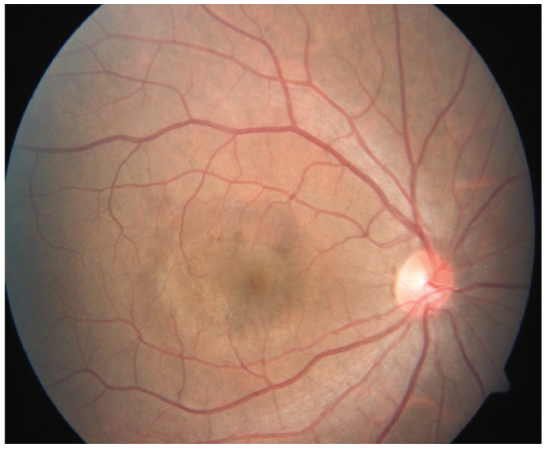

Figure 5. Fundus photograph showing complete clearing of hemorrhage with normal looking posterior pole at 7 days post-C3F8 gas injection

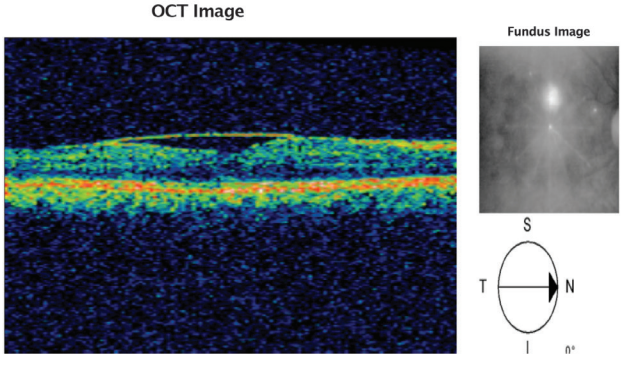

Figure 6. Optical coherence tomography showing normal foveal contour and architecture with overlying inner limiting membrane fold

To the best of our knowledge, this is the first reported case of dengue maculopathy complicated by sub-ILM premacular hemorrhage treated successfully with the minimally invasive novel technique of pneumatic tamponade with prone positioning, resulting in faster and complete visual recovery with no residual adverse effects in a soldier on active duty. However, prospective, randomized trials with large patient numbers will be required to validate the effectiveness and safety of pneumatic tamponade as a treatment modality for premacular sub-ILM hemorrhage in dengue maculopathy.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ashok Kumar, Concept: Ashok Kumar, Vikas Ambiya, Design: Ashok Kumar, Data Collection or Processing: Vinod Kumar Baranwal, Amit Arora, Analysis or Interpretation: Vinod Kumar, Baranwal, Amit Arora, Literature Search: Gaurav Kapoor, Writing: Ashok Kumar, Amit Arora.

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